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VOL. 47 JANUARY, 1944 NO. 1

Original Communications

THE HARMFUL INFLUENCE OF PREGNANCY ON ADVANCED TUBERCULOSIS AS MODIFIED BY COLLAPSE THERAPY*

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(From the Wawa Chest Hospital, Wawa, Pa.)

IT IS generally recognized that in a significant number of patients pregnancy can have a harmful influence on the evolution of tuberculosis. This may become clinically manifest during the early months of pregnancy or during the post-partum period and may endanger the life of the mother. Many women trace the clinical onset of their tuberculosis to a period during pregnancy or following delivery; therefore, the combination of tuberculosis and pregnancy continues to be a subject of critical interest.[1-4] Although it is appreciated that pregnancy in the tuberculous woman is a matter of carefully judging many factors (physiologic, social, economic, as well as pathologic), two general rules have been laid down for the guidance of females afflicted with advanced tuberculosis: (1) Women with advanced tuberculosis should not marry; (2) Married women with advanced tuberculosis should not conceive. This is especially true if there has been recent activity.

Since collapse therapy has unquestionably improved the outlook of the tuberculous patient in general, it is of prime importance to re-evaluate the prognosis of the parturient woman with advanced tuberculosis under conditions of modern therapy to determine to what extent the above mentioned views need modification. There are increasing reports of women with advanced tuberculosis who have come through one or more pregnancies without harm once the disease in the lungs was successfully controlled with pneumothorax or thoracoplasty, or some other form of collapse therapy.[5-9]

*Presented before The Obstetrical Society of Philadelphia, December 3, 1942.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

The present study is an effort to determine the immediate and long-term effects of pregnancy, and the responsibilities which follow, upon advanced tuberculosis in a single consecutive series of twenty-six white women who received collapse therapy to control the tuberculosis, before giving birth to one or more children. The collapse therapy procedures employed to control the tuberculosis in this series were: pneumothorax—unilateral (20), bilateral (6), pneumonolysis (7), maintenance oleothorax (7), and phrenic nerve interruption (6), in various combination. These patients have been under constant clinical and roentgenologic observation for varying periods during the past fifteen years. The minimum period of observation has been sixteen months; the maximum, fifteen years; the average for the group was approximately nine years.

Description of Material

All were private patients of about the same social and economic level. I know the great majority of these patients intimately and have kept accurate and detailed notes with repeated fluoroscopic and x-ray studies. They were cooperative and interested in their health. With stated exceptions, they undertook marriage and pregnancy only after careful consideration and at a time when they had every reason to feel reasonably secure in their health. Their intelligence and morale were on a higher plane than that usually encountered in clinic patients. Pregnant white and colored women receiving collapse therapy in the clinic, and pregnant tuberculous women who received no collapse therapy, are not included in this presentation. These are points worth stressing; for, in a sense, by limiting the study to such a selected group, the results should represent generally the more favorable side of the combination of pregnancy and tuberculosis.

With one exception (Case 23, Fig. 6), all patients had cavity formation and tubercle bacilli in the sputum when first seen. In nine, the disease was unilateral; in six, predominantly unilateral; and in eleven, it was definitely advanced in both lungs. Ten of these women were married and sixteen were single when first seen, but the latter group subsequently married and reared families. Twenty-two women were primiparas and four multiparas when first placed under treatment for tuberculosis. These women had forty-eight known pregnancies following the establishment of collapse therapy and gave birth to forty children.

Fifteen women gave birth to one child, nine to two children, one to three children (one set of twins) and one to four children. The other pregnancies terminated in four abortions and five miscarriages. The average period of observation after the first pregnancy was—58 months, second pregnancy—41 months, third pregnancy—45 months, and after the fourth pregnancy—12 months. The women received their obstetrical care at the hands of twenty different obstetricians. None of the women nursed their babies.

These cases fall into three groups: 1. Patients in whom tuberculosis was recognized and treated successfully with collapse therapy before pregnancy—22 cases. 2. Patients in whom the tuberculosis was recognized, but treated unsatisfactorily with collapse therapy (inability to close cavities) before pregnancy set in—3 cases. 3. Patients in whom the tuberculosis was first recognized during pregnancy—2 cases (one of

these patients received pneumothorax, subsequently became pregnant, and is again considered in group 1 as a new case).

Patients in Whom Tuberculosis Was Recognized and Treated Successfully With Collapse Therapy Before Pregnancy

Twenty-two patients with advanced tuberculosis were successfully treated with collapse therapy before becoming pregnant. Two to twenty-seven months elapsed before the tuberculosis was stabilized by the collapse and the sputum was rendered free of tubercle bacilli. The average for the group was 5.5 months. An additional 8 to 26 months elapsed from stabilization of the tuberculosis and disappearance of tubercle bacilli from the sputum to the termination of the first pregnancy, with an average for the group of 13 months. Approximately 40 months elapsed between the first and second pregnancies and 27 months between the third and fourth pregnancies. In the case of the sixteen women who were single when first seen, 29 months elapsed on the average from stabilization of the disease and negative sputum to date of marriage. It is apparent from these figures that, with the one exception noted below, marriage and pregnancy were undertaken only after careful consideration at a time when there was ample justification to regard the tuberculosis as arrested or "cured" according to accepted standards. Notwithstanding these precautions, there was evidence of increased disease in 4, or 18 per cent of the group, as a direct result of pregnancy.

In three of the four patients, increased disease, of sufficient clinical importance to require treatment—bed rest in one, and pneumothorax therapy in two, first became evident within two months *following* childbirth. All three responded to treatment and did well. The fourth patient developed increased disease during the *early months* of a pregnancy which terminated spontaneously at three months. The increased disease produced no ill effects and required no special treatment. It underwent spontaneous retrogression upon termination of pregnancy.

A detailed discussion of the various subgroups, comprising these twenty-two patients, is in order.

(a) In nine patients (Figs. 1, 2, 3, 4, 5, 6, 7, 8, 9), the disease was confined to one lung when first seen with no x-ray evidence of tuberculosis in the contralateral lung. All received pneumothorax therapy (in four cases, Figs. 4, 5, 8, 9, the pneumothorax was later replaced with maintenance oleothorax). In each instance, all cavities were closed, the positive sputum rendered negative, and the patient restored to good health before pregnancy set in. All nine did well and their clinical course was entirely uneventful.

Four of these patients (Figs. 5, 6, 7, 9) had one pregnancy and one baby each, of which one baby died at premature birth at eight months. One patient (Fig. 9) is pregnant a second time. Three patients (Figs. 1, 2, 4) had two pregnancies and two healthy babies each. One (Fig. 3) had three pregnancies, the first of which was a miscarriage at two months. Her other two pregnancies were full term and resulted in two healthy babies. One patient (Fig. 8) had three pregnancies, the first two of which were miscarriages at two months each and the third was entirely normal, resulting in the birth of a healthy girl. This patient, incidentally, had a double vagina and uterus.

(b) In five patients (Figs. 10, 11, 12, 13-15, 16-18), the disease was confined almost entirely to one lung, but there was x-ray evidence of tuberculosis in the contralateral lung, considered of no clinical importance at the time and consisting for the most part of moderately dense spots and

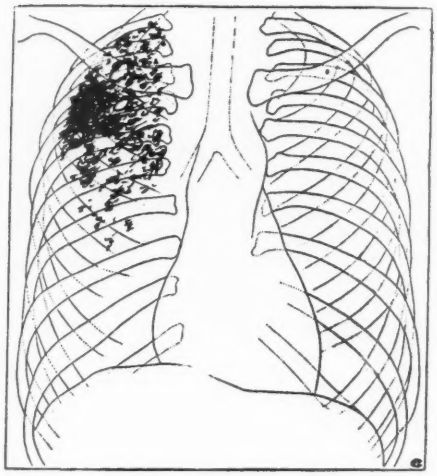

Fig. 1.—Case 1.

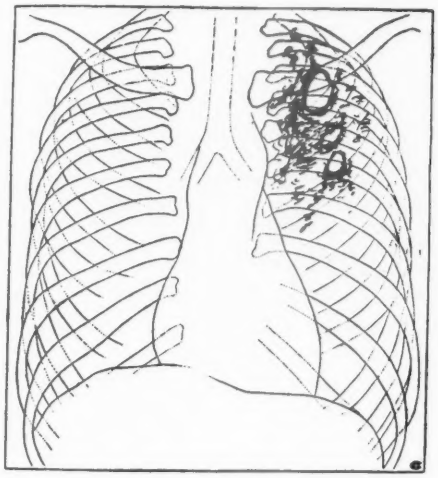

Fig. 2.—Case 5.

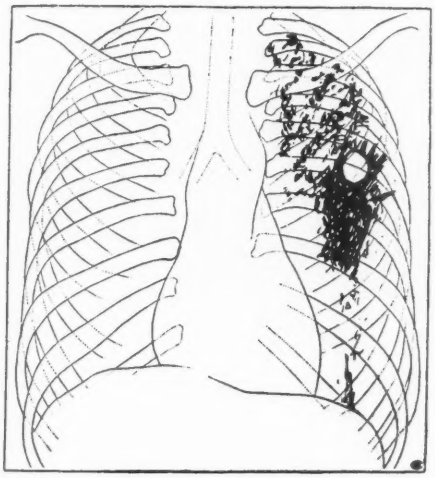

Fig. 3.—Case 11.

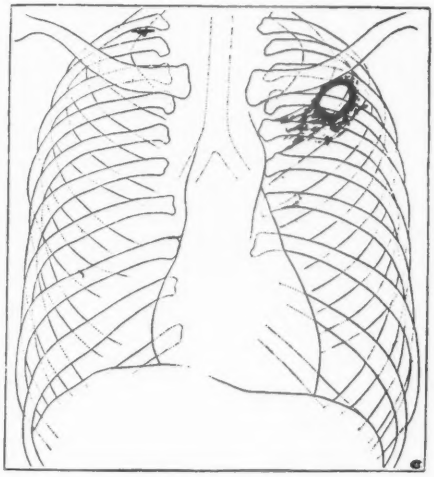

Fig. 4.—Case 18.

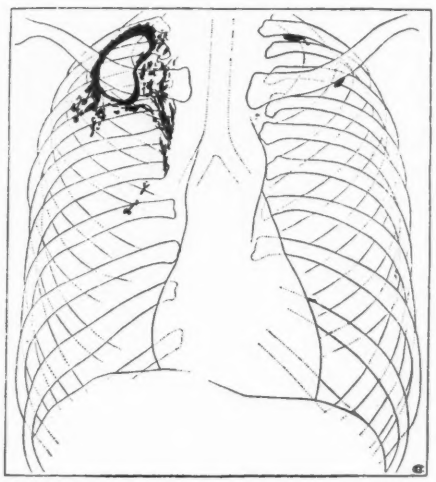

Fig. 5.—Case 19.

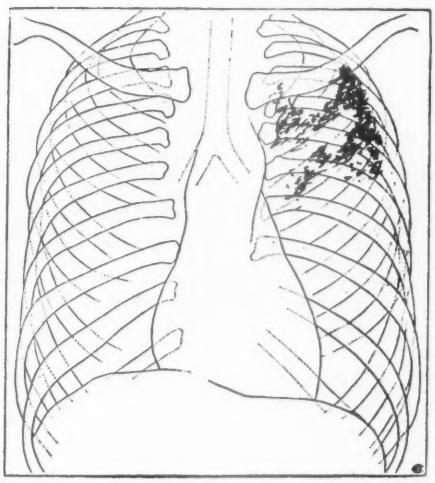

Fig 6.—Case 23.

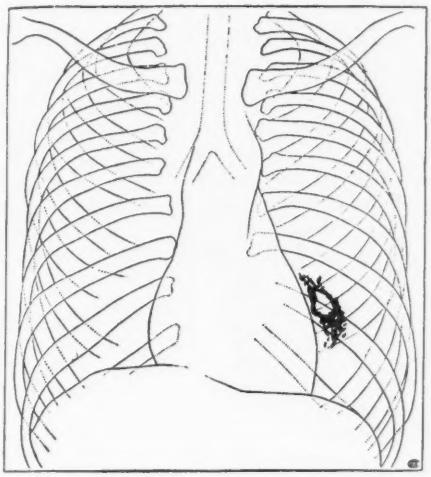

Fig. 7.—Case 24.

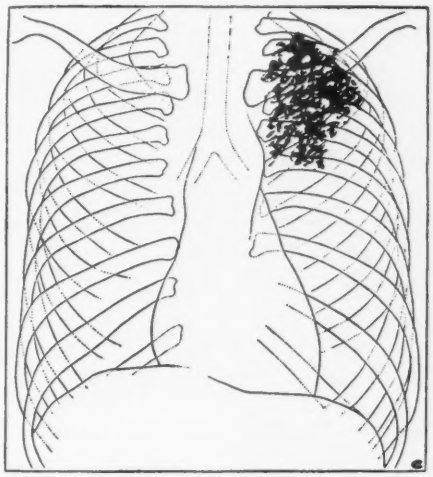

Fig. 8.—Case 25.

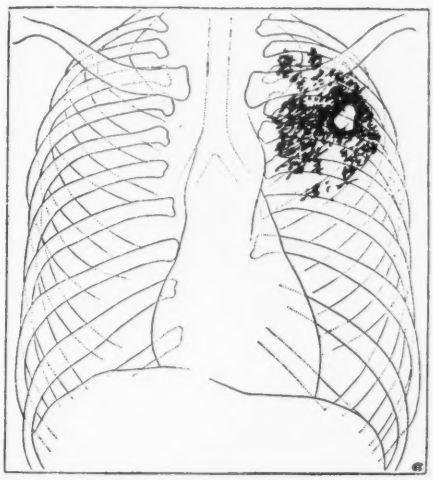

Fig. 9.—Case 26.

Patients in Whom Tuberculosis Was Recognized and Treated Successfully with Collapse Therapy Before Pregnancy*

Group a.—Cases 1, 5, 11, 18, 19, 23, 24, 25, and 26 (Figs. 1, 2, 3, 4, 5, 6, 7, 8, and 9). Under observation since July 23, 1928, July 28, 1929, July 14, 1932, June 30, 1936, July 17, 1936, July 26, 1936, March 2, 1938, April 8, 1938, March 23, 1939, respectively.

In these patients the disease was confined to one lung when first seen with no x-ray evidence of tuberculosis in the contralateral lung. All received pneumothorax therapy. In each instance all cavities were closed, the positive sputum rendered negative, and the patient restored to good health before pregnancy set in. All women did well and their clinical course was entirely uneventful.

*Cases are numbered consecutively in the order in which they presented themselves for treatment.

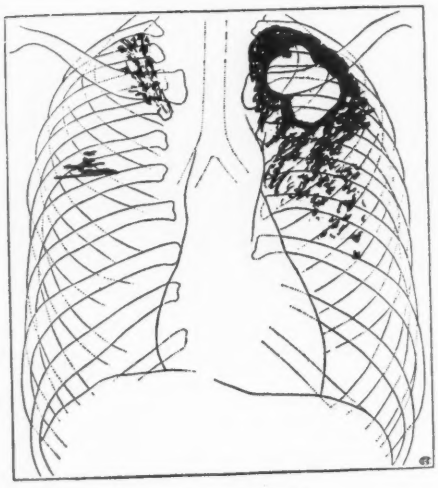

Fig. 10.—Case 14.

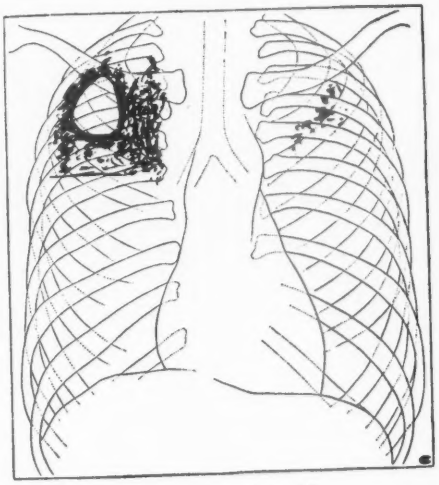

Fig. 11.—Case 15.

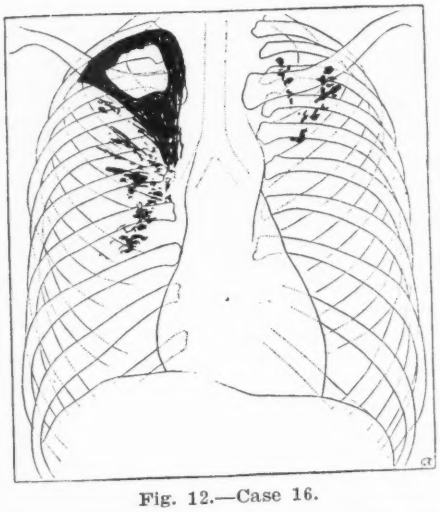

Fig. 12.—Case 16.

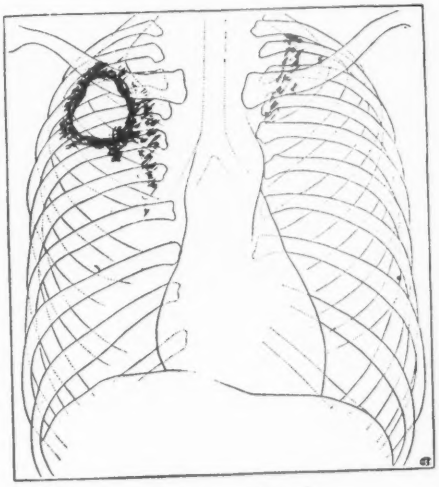

Fig. 13.—Case 3.

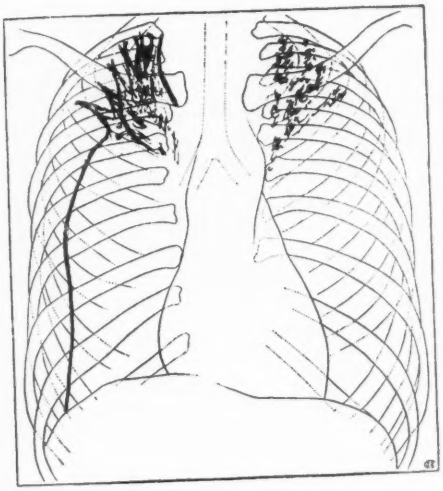

Fig. 14.—Case 3.

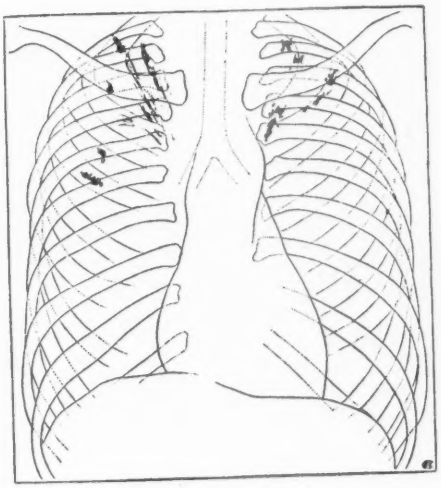

Fig. 15.—Case 3.

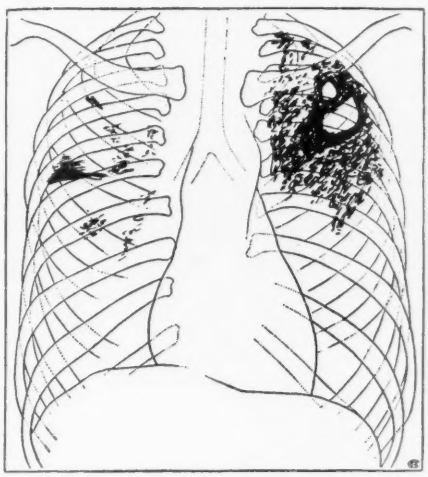

Fig. 16.—Case 10.

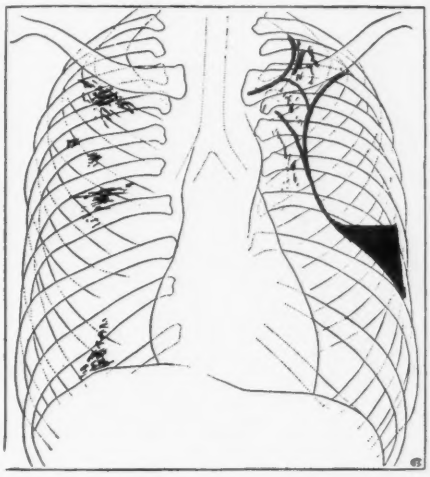

Fig. 17.—Case 10.

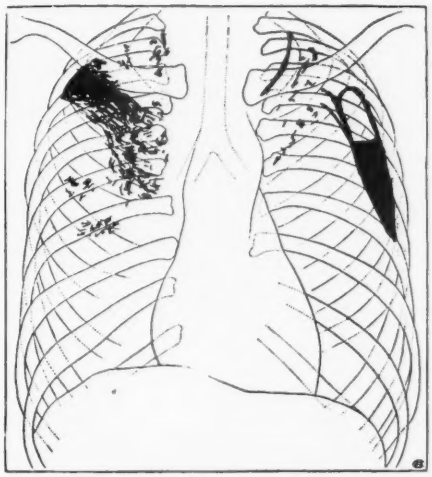

Fig. 18.—Case 10.

Patients in Whom Tuberculosis Was Recognized and Treated Successfully with Collapse Therapy Before Pregnancy

Group b.—Cases 14, 15, and 16 (Figs. 10, 11, and 12); Cases 3 (Figs. 13, 14, 15) and 10 (Figs. 16, 17, 18). Under observation since November 20, 1933, July 21, 1934, April 28, 1935; June 28, 1929 and June 1, 1932, respectively.

In these patients the disease was confined almost entirely to one lung, but there was x-ray evidence of tuberculosis in the contralateral lung, considered of no clinical importance at the time and consisting for the most part of moderately dense spots and fibrous strands. Only the disease in the more involved lung was treated with pneumothorax therapy before pregnancy set in. In every instance the disease was well controlled in both lungs, with all cavities closed, and the sputum rendered negative long before pregnancy.

Three of the five patients (Cases 14, 15, and 16; Figs. 10, 11, and 12) did well and had an uneventful clinical and roentgenologic history.

Two of the five patients (Case 3; Figs. 13, 14, and 15 and Case 10; Figs. 16, 17, and 18) had definite x-ray evidence of new disease in the "good" lung as a direct result of the pregnancy. In Case 3, this occurred two months following delivery (Fig. 14) but underwent spontaneous improvement (Fig. 15). In Case 10, new disease first appeared three weeks after delivery (Fig, 17), gradually became worse during the next eight months (Fig. 18), at which time pneumothorax therapy was instituted to bring the disease under control.

fibrous strands. Only the disease in the more involved lung was treated with pneumothorax therapy before pregnancy set in. In two (Figs. 11, 12), the pneumothorax was supplemented with a pneumonolysis operation and the pneumothorax later replaced with maintenance oleothorax. In every instance, the disease was well controlled in both lungs, with all cavities closed, and the sputum rendered negative long before pregnancy.

Three of the five patients (Figs. 10, 11, 12) did well and had an uneventful clinical and roentgenologic history. Two of these three patients (Figs. 10, 11) had one pregnancy and one healthy baby each; one of them (Fig. 10) is pregnant a second time. The third patient (Fig. 12) had three pregnancies, the first of which was terminated artificially at two months because of an unreasonable fear on the part of the patient of what the pregnancy might do to the tuberculosis. The second and third pregnancies were full term and uneventful and resulted in two healthy children.

Two of the five patients (Figs. 13-15 and 16-18) had definite x-ray evidence of new disease in the "good" lung as a direct result of the pregnancy. In one patient (Figs. 14 and 15), this occurred two months following delivery. The new disease was not accompanied by clinical signs or symptoms and would not have been detected except for the x-ray. The disease subsided spontaneously and no therapy was required. The patient suffered no ill effects. In the other patient (Figs. 16-18) an increase in disease in the "good" lung was first noted in the x-ray film three weeks after the birth of the second baby (the first pregnancy was entirely uneventful) but at the time gave rise to no signs or symptoms and apparently required no treatment. It was entirely an x-ray observation. Gradually, however, the disease in the "good" lung became sufficiently important clinically to warrant pneumothorax treatment. This patient has done well with bilateral pneumothorax therapy and at present (three years after all pneumothorax treatment has been discontinued) is enjoying excellent health.

(c) In three patients (Figs. 19, 20, 21), the disease was bilateral, but advanced in both lungs. These patients were treated successfully with bilateral pneumothorax therapy. In two the pneumothorax was made complete with pneumonolysis and later replaced with bilateral maintenance oleothorax before the patients became pregnant. All did well and their clinical course was entirely uneventful. Two of these patients (Figs. 20 and 21) had one pregnancy and one baby each, the third (Fig. 19) had three pregnancies and two healthy babies. Her second pregnancy was terminated artificially at two months.

(d) In three patients (Figs. 22, 23, 24-26), the disease was bilateral and advanced in both lungs. Before the patients became pregnant, the lungs were treated successfully with pneumothorax therapy on the more involved side and with phrenic nerve interruption on the other. In all instances, the tuberculosis in the two lungs was definitely controlled and the sputum was negative many months before pregnancy set in. Two (Figs. 22, 23) had an entirely uneventful tuberculosis history following pregnancy. One of these two patients (Fig. 22) had four pregnancies and four living children; the other patient (Fig. 23), two pregnancies, the first of which was full term and the second an abortion at two months.

The third patient in this subgroup (Figs. 24-26) had four pregnancies. She had an extension of the disease in the lung treated with phrenic nerve interruption during the early months of the third preg-

nancy. Her first pregnancy was entirely uneventful and she gave birth to a full-term baby. The second pregnancy terminated spontaneously at eight months in the birth of twins. Both children died shortly after birth, but the mother's health remained good. During the first two months of the third pregnancy, there was found in the lung previously treated successfully with phrenic nerve interruption x-ray evidence of increased disease, sufficiently serious to require bed rest treatment for several months. However, this pregnancy terminated spontaneously at three months and the tuberculosis quieted down almost at once. Six months later, this patient again became pregnant, again had a miscarriage at three months, but without harmful effect on the tuberculosis. Only during the third pregnancy was there evidence of increased disease and this in the lung treated with phrenic nerve interruption.

(e) In two patients (Figs. 27 and 28-30), the disease was bilateral and advanced in both lungs when first seen. Pneumothorax was used successfully on the more involved side and no collapse therapy whatever was used on the other side before pregnancy set in. In one of these (Fig. 27), the disease in the contralateral lung responded so well to bed rest treatment during the time required to control the disease in the worse lung with pneumothorax, that bilateral collapse therapy was not considered necessary. This patient went through three pregnancies. The first two were full term and the third was an abortion at two months. Her clinical course was entirely uneventful.

The other patient (Figs. 28-30) became pregnant unexpectedly two months after pneumothorax was instituted on the right or more involved side at a time when the disease was not considered stabilized in either lung. The danger of the pregnancy activating the tuberculosis, particularly in the uncollapsed lung, was fully appreciated; but after careful consideration, the patient, who was anxious to have the child, was permitted to go to term with the understanding that bilateral collapse therapy might be necessary. She was kept on bed rest throughout the entire pregnancy and treated as if she had active tuberculosis. In due course, with nothing unusual happening, she was delivered of a healthy male baby. An x-ray, four weeks after delivery, showed no change in the character of the disease. Two months later, however, there was a very definite spread of the tuberculosis in the left or uncollapsed lung and clinical symptoms of active disease made their appearance. Bilateral pneumothorax was promptly instituted and the disease controlled. This patient is still receiving bilateral pneumothorax—six years later—and is leading a normal active life, works, and helps to support the family. The baby is healthy.

Patients in Whom the Tuberculosis was Recognized but Treated Unsatisfactorily (Inability to Close Cavities) Before Pregnancy

Three patients in this series (Figs. 31, 32, 33) received collapse therapy, but the cavities were not closed nor the sputum rendered free of tubercle bacilli at the beginning of pregnancy. Not one of these patients did well. One is dead, one is in poor health, and the other, when last observed (October 28, 1936), was considered a hopeless case of tuberculosis. In two of these patients, the pregnancy was not immediately followed by an increase in the disease, but the fact remains that they were all doing well prior to pregnancy and began doing poorly sometime after childbirth.

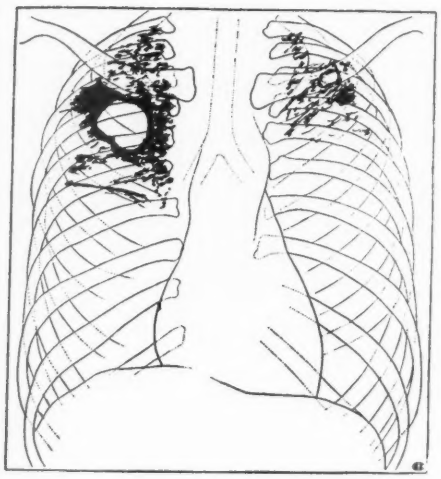

Fig. 19.—Case 6.

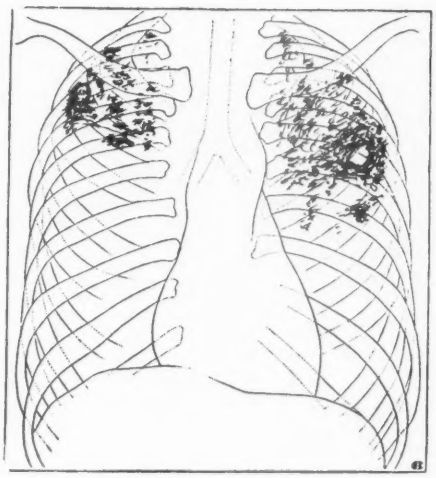

Fig. 20.—Case 21.

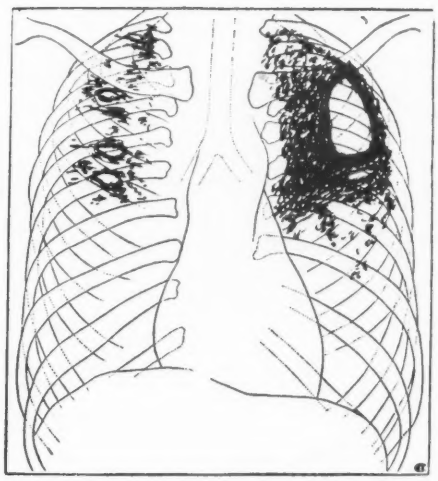

Fig. 21.—Case 22.

Patients in Whom Tuberculosis Was Recognized and Treated Successfully with Collapse Therapy Before Pregnancy

Group c.—Cases 6, 21, and 22 (Figs. 19, 20, and 21). Under observation since September 20, 1930, April 2, 1937, and April 5, 1937, respectively.

In these patients the disease was bilateral, but advanced in both lungs. All three were treated successfully with bilateral pneumothorax therapy before the patients became pregnant. All did well and their clinical course was entirely uneventful.

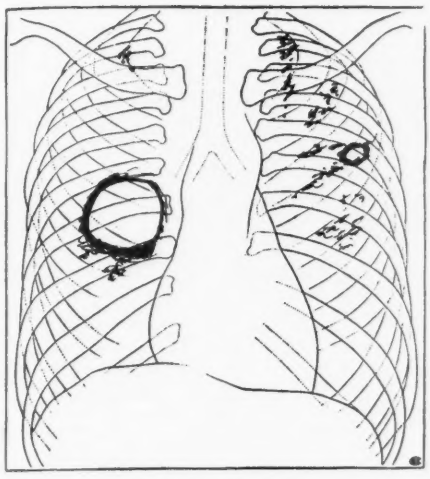

Fig. 22.—Case 7.

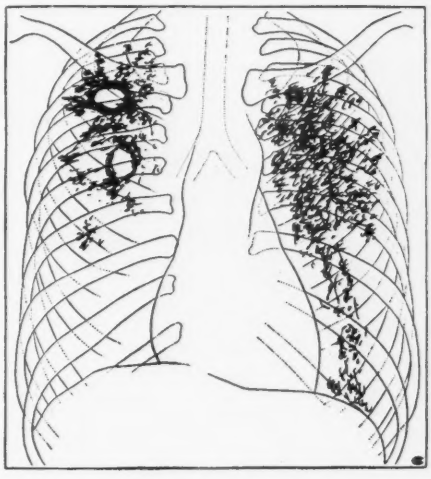

Fig. 23.—Case 8.

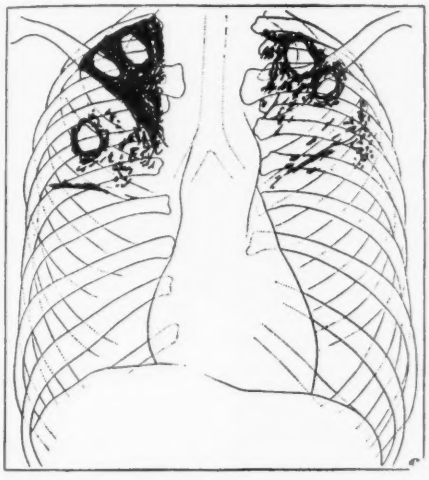

Fig. 24.—Case 9.

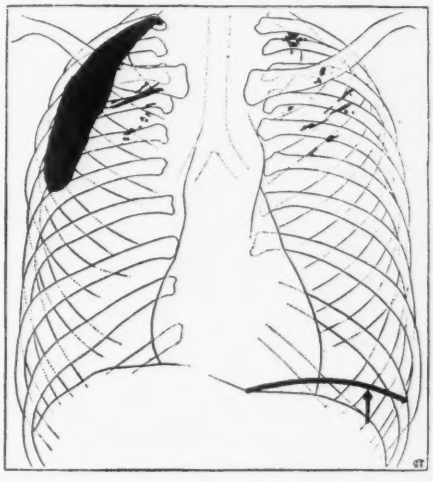

Fig. 25.—Case 9.

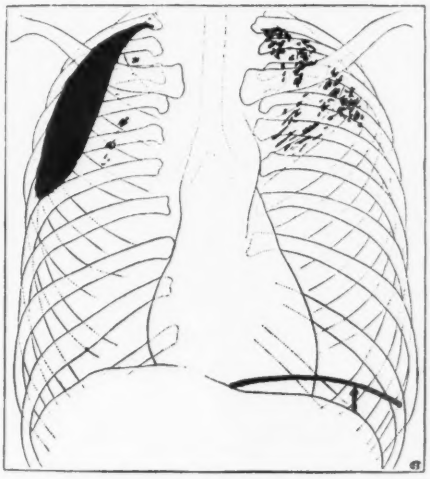

Fig. 26.—Case 9.

Patients in Whom Tuberculosis Was Recognized and Treated Successfully with Collapse Therapy Before Pregnancy

Group d.—Cases 7, 8, and 9 (Figs. 22, 23, and 24, 25, 26). Under observation since October 7, 1930, April 17, 1931, and May 20, 1932, respectively.

In these patients the disease was bilateral and advanced in both lungs. Before the patients became pregnant, the lungs were treated successfully with pneumothorax therapy on the more involved side and with phrenic nerve interruption on the other. Cases 7 and 8 (Figs. 22 and 23) had an entirely uneventful tuberculosis history following pregnancy.

In Case 9 (Figs. 24, 25, and 26), there was extension of disease in the lung treated with phrenic nerve interruption during the early months of the third pregnancy (Fig. 26—pregnant six weeks), sufficiently serious to require bed rest treatment for several months. The other pregnancies were entirely without effect on the tuberculosis (Fig. 25, one month after first miscarriage and twenty-five months after second delivery).

In retrospect, the disease in each instance was neither more intense nor more extensive when first seen than in some of the patients in whom adequate collapse could be established before pregnancy set in. These three patients serve as excellent controls and reveal in striking contrast the risk of pregnancy to women with advanced tuberculosis not previously controlled with adequate collapse therapy. The case histories follow:

Case No. 17 (Fig. 33), W. H., aged 28, first consulted me on January 22, 1935, but was known to have had tuberculosis since 1926. Following the diagnosis in 1926, she was "cured" without collapse therapy and later worked as a nurse in a sanatorium for about two years and made a fair clinical recovery. In 1929, she married and in 1930 gave birth to a baby without any apparent ill effects. She maintained reasonably good health until the birth of the second baby in August, 1933. She has not been well since. At first, she returned to "bed rest" and although she regained twenty-seven pounds, she continued to cough and expectorate and at times would expectorate blood. In January, 1935, I instituted pneumothorax therapy on the left side and on May 25, 1943, crushed the right phrenic nerve. There was gratifying and continued clearing of the disease in both lungs during the following months as a direct result of the collapse therapy, but one cavity in the upper part of the left lung, although reduced in size, failed to close because of extensive inoperable adhesions. In October, 1935, she became pregnant. Therapeutic abortion was advised, but the patient refused on religious grounds so there was nothing to do but carry her to term. Unfortunately, she did not do at all well and her health went steadily down with each passing month of pregnancy. On April 17, 1936, she gave birth to a premature infant of seven months, who died within a few hours. The mother died of progressive tuberculosis one month later. There is no question in my mind that the pregnancy was the one deciding factor which immediately altered her prognosis for the worse.

Case No. 13 (Fig. 32), C. D., aged 22. This patient traced the onset of her tuberculosis to her last pregnancy. She became ill in 1932 with respiratory symptoms, which never left her, six weeks after giving birth. She was referred to me on April 27, 1933, and at that time there was extensive involvement of the entire right lung with several cavities present. There was also disease in the left lung limited to the middle third and consisting of grouped flocculent spots, but no cavities. She weighed eighty pounds and was in poor health. Pneumothorax therapy was established on the right and she was kept in bed. There followed striking and rapid improvement during the next five months so that by November, 1933, she weighed ninety-nine pounds and her cough and expectoration were definitely reduced. The disease in the left lung was noticeably better, but one cavity in the right upper lobe could not be closed with the pneumothorax because of extensive inoperable adhesions. In the light of subsequent events, November, 1933, was the peak month of improvement. During the next year, she just about held her own, with the cavity in the right apex remaining open. It was under these circumstances that she became pregnant, nineteen months after pneumothorax was instituted. She refused an abortion and on September 21, 1935 gave birth to a healthy baby girl. As determined by x-ray, there was no apparent damage to the lungs for at least three months following childbirth. Clinically, however, she was never the same. Her health gradually dwindled. By May, 1936, there was more disease in the left

lung, the uncollapsed cavity in the right apex was larger, her weight was reduced to eighty-one pounds, and the prognosis was considered hopeless. Her condition was no better when I saw her last on October 28, 1936. Here, again, there is no question but that the prognosis remained reasonably good until she became pregnant and that it became virtually hopeless following delivery. The only difference in this case as contrasted with some of the patients who did well during and after pregnancy was in the quality of the collapse. Her disease was not anatomically well controlled with the pneumothorax when she became pregnant.

Case No. 12 (Fig. 31), M. W. This patient, aged 26, was known to have had tuberculosis as far back as 1928. I first saw her on July 8, 1932. At the time there was involvement of both lungs, limited to the upper lobes with a cavity at the right apex. The disease was moderately active. Pneumothorax was instituted on the right side, but was ineffectual in closing the cavity. This treatment was abandoned and replaced with a temporary phrenic nerve interruption. She improved steadily during the next year, regained much of her previous health and moved to another city. The cavity at the right apex, although smaller, was still present. In 1938, her only child, a boy eleven years old, was drowned and she decided to have another baby. She was apparently in good health and her doctor assured her it was safe. She vomited a great deal during the early months of pregnancy and lost about twenty-five pounds. In spite of this, her general health apparently remained good, and on May 17, 1939, she gave birth to a healthy baby. Her health remained apparently unchanged until March, 1941, when the tuberculosis became definitely active and she again consulted me on July 18, 1941. At the time, there was a large cavity at the right apex much larger than in 1932. The disease in the left lung, however, appeared healed and consisted, for the most part, of calcified spots. Unfortunately, there are no serial x-ray studies available before and after childbirth, but it is fair to assume from the very nature of the case that the cavity was open all through pregnancy. On close questioning, she did not have "good health" following childbirth, and it is quite probable that her tuberculosis gradually became worse following the birth of the baby. The disease was of the chronic, fibro-ulcerative type with relatively few symptoms. Many months must have elapsed before the cavity reached the size it ultimately did when she again consulted me. At present, this patient is going from bad to worse and will most certainly die of tuberculosis. This case, again, illustrates the unfavorable influence of pregnancy on advanced tuberculosis, not adequately controlled with collapse therapy. Phrenic nerve interruption is not enough.

Patients in Whom Tuberculosis Was First Recognized During Pregnancy

The diagnosis of clinically active tuberculosis and pregnancy always presents a serious problem, requiring prompt and energetic action. The course of the disease is often markedly aggravated and the tuberculosis may constitute a real threat to life. The accepted procedure in such cases is therapeutic abortion, during the first trimester; or, if the patient presents herself near the stage of fetal viability or close to term, careful medical and obstetric supervision, modified as individual requirements may dictate.

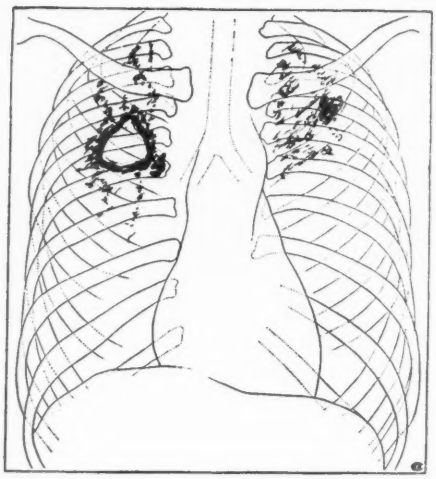

Fig. 27.—Case 4.

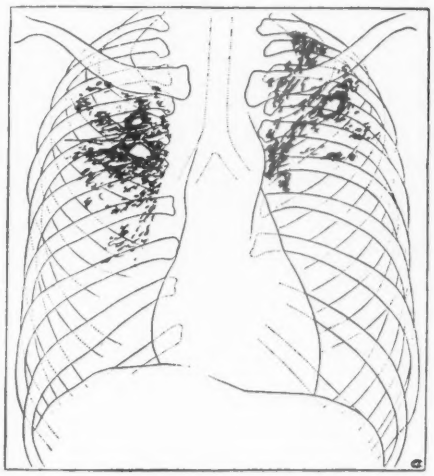

Fig. 28.—Case 20.

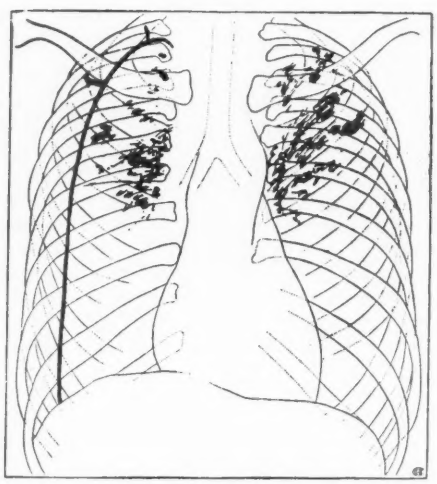

Fig. 29.—Case 20.

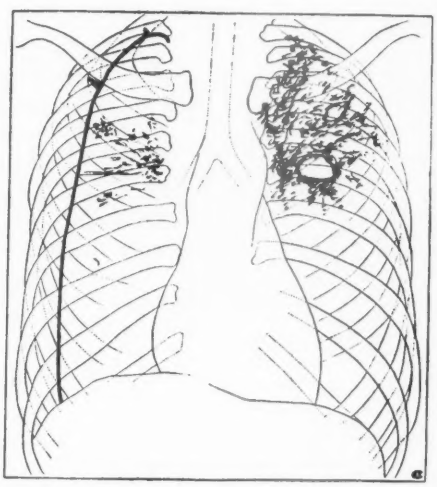

Fig. 30.—Case 20.

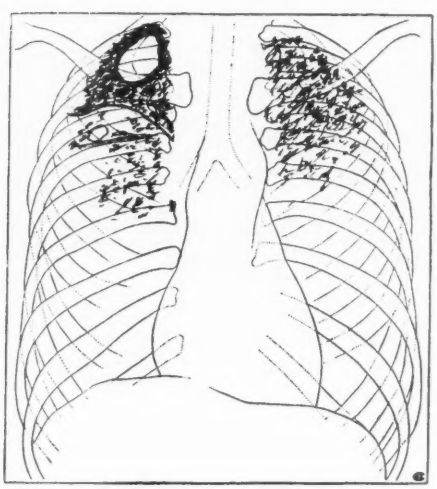

Fig. 31.—Case 12.

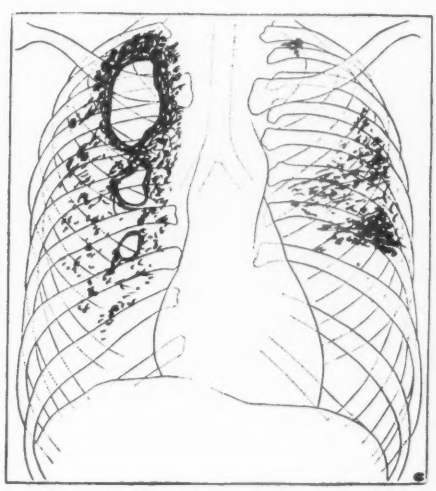

Fig. 32.—Case 13.

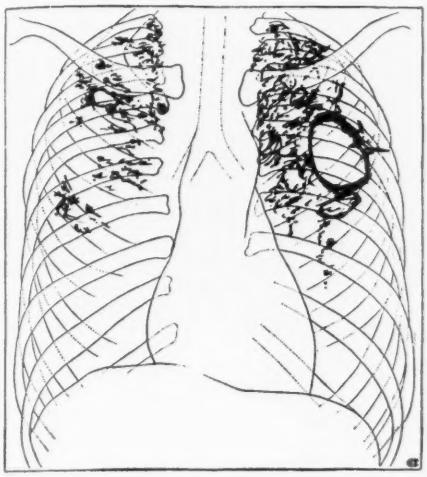

Fig. 33.—Case 17.

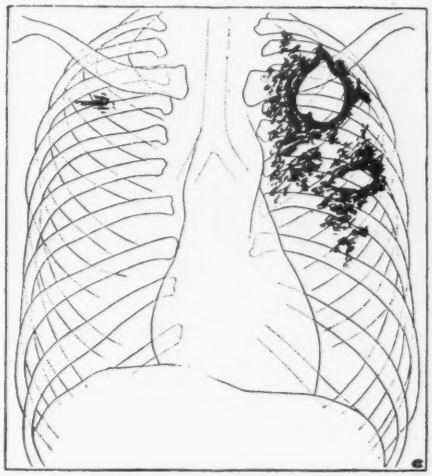

Fig. 34.—Case 2.

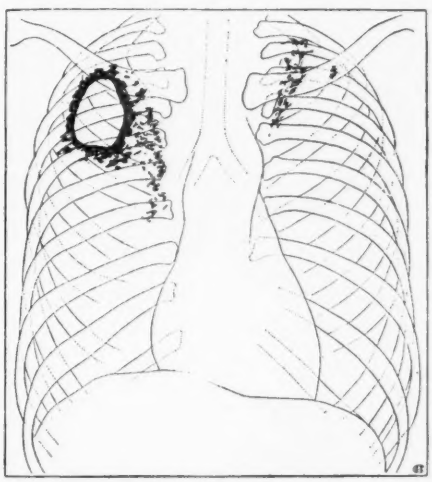

Fig. 35.—Case 3.

Patients in Whom Tuberculosis Was Recognized and Treated Successfully with Collapse Therapy Before Pregnancy

Group e.—Cases 4 and 20 (Figs. 27, and 28, 29, 30). Under observation since June 8, 1929 and October 24, 1936, respectively.

In these patients the disease was bilateral and advanced in both lungs when first seen. Pneumothorax was used successfully on the more involved side and no collapse therapy whatever on the other side before pregnancy set in. In Case 4 (Fig. 27), the clinical course was entirely uneventful; in Case 20, (Figs. 28, 29, and 30), new disease appeared in the untreated lung two months after delivery and required pneumothorax therapy (Fig. 30). Fig. 29 shows the condition of the lungs when the patient was four months pregnant.

Patients in Whom the Tuberculosis Was Recognized but Treated Unsatisfactorily Before Pregnancy

Cases 12, 13, and 17 (Figs. 31, 32, and 33). Under observation since July 8, 1932, April 5, 1933, and January 22, 1935, respectively.

In these patients the cavities were not closed and the sputum rendered free of tubercle bacilli before pregnancy set in. All did poorly. For details, see text.

Patients in Whom Tuberculosis Was First Recognized During Pregnancy

Cases 2 and 3 (Figs. 34 and 35). Under observation since July 28, 1928 and June 28, 1929, respectively.

Case 2 (Fig. 34) was treated with artificial pneumothorax and no interference with pregnancy; Case 3 (Fig. 35), with therapeutic abortion, followed by pneumothorax therapy. Both patients did well.

Two patients in this series (Cases 2 and 3, Figs. 34 and 35) had active, advanced tuberculosis, first recognized during pregnancy. One was treated with therapeutic abortion, followed by pneumothorax therapy; the other, by immediate pneumothorax and no interference with pregnancy. Both patients did well. It is therefore of interest to present these cases in some detail.

Case No. 2, R. S., aged 22, first came under my observation on July 20, 1928, suffering with advanced active tuberculosis of the left lung with cavity formation and sputum positive for tubercle bacilli. Râles were heard to the fourth rib, anteriorly. The patient also complained of nausea and vomiting with pain over the right lower abdomen, and no menses for the past two months. These symptoms, however, received little consideration at the time and were believed to be due to probable ileocecal tuberculosis. The patient was placed on calcium chloride therapy intravenously and in due time the nausea and vomiting disappeared. During the first six weeks of observation the temperature, cough, and expectoration continued to increase in severity and the patient was losing steadily in weight. On September 1, 1928, artificial pneumothorax was instituted on the left side and almost immediately the patient began to show definite improvement. Temperature and pulse soon returned to normal, cough and expectoration were greatly reduced, and tubercle bacilli disappeared from the sputum. The patient began to gain in weight and naturally felt greatly elated over the turn of events. On November 8, 1928, the patient called my attention to the fact that her abdomen was increased in size and made the suggestion that she was pregnant. Careful examination soon confirmed the diagnosis and for the first time it was realized that the patient was pregnant when first seen and that the nausea and vomiting were not due to probable ileocecal tuberculosis, as was first believed, but to pregnancy. Of course, it was too late to interrupt gestation, and again the patient was in such splendid shape clinically, that she was advised to go through with it. Everything went along smoothly until January 10, 1929, when she suddenly developed high fever of 104 degrees with moderate pain in the right upper abdomen. A diagnosis of right-sided pyelitis was established and the patient treated accordingly with satisfactory results. At the same time, fluid appeared in the left pleural cavity, which required several aspirations. On March 4, 1929, the patient delivered a healthy male child. The convalescence was uneventful. Although the sputum became positive for a short time after the delivery, the tubercle bacilli again disappeared. The patient continued to gain in weight and strength and left my care as an arrested case of tuberculosis on July 16, 1929. The last report from the patient in 1932 stated that she was enjoying good health, that the baby was in splendid condition, and that she was still continuing with artificial pneumothorax treatment.

It is highly probable that had I realized that this patient was pregnant when she first came under my care, she would have been aborted.

Case No. 3, I. G., aged 24, first came under observation for tuberculosis in May, 1929, at which time she was known to be three months pregnant. Both x-ray and physical findings revealed softening and excavation of the right upper lobe. The sputum was positive for tubercle bacilli and clinically, there were cough, expectoration, fever, and night sweats. During the two weeks prior to the diagnosis of tuberculosis, the patient had lost nine pounds in weight and was confined to bed. Because of the severe character and apparent acute onset of the tuberculosis, a

therapeutic abortion was performed on June 1, 1929. My contact with the patient began on June 19, 1929. The patient was still manifesting all the signs and symptoms of acute tuberculosis, and artificial pneumothorax was instituted on the right side. In a short time, her temperature returned to normal, cough and expectoration practically disappeared, and her weight picked up steadily. Subsequently, she had two children while under pneumothorax treatment (discussed along with patients in group one).

This experience certainly raises the question of the wisdom of abortion in all cases of active tuberculosis and pregnancy without first considering artificial pneumothorax. If a good anatomical collapse can be obtained, and this can often be determined within a month or two, the patient can be permitted to go to term. Even thoracoplasty has been done successfully during pregnancy.[9]

Discussion

One striking feature emerges from a study of these twenty-six case histories, namely, the freedom from reactivation of advanced tuberculosis in a lung, the diseased area of which was anatomically well collapsed before pregnancy. Every exacerbation or extension of disease in this series was always in the lung not collapsed, poorly collapsed, or treated with phrenic nerve interruption. The extent and severity of the original disease, whether confined to the right or left lung, or both lungs, were not determining factors. The all important consideration was the quality of the collapse, particularly whether all cavities were closed and the collapse well maintained. Women in whom this was true came through pregnancy without harm and were able to lead normal lives the same as any nontuberculous mother.

Stabilized tuberculosis not controlled with collapse therapy presented an entirely different problem. Fibrous strands, or thickened pleura with or without salients into the lung structure, or calcified spots were of no clinical importance. Such patients did well.

When the tuberculosis, however, extended beyond these limits and was not controlled with pneumothorax, serious relapses followed in some instances. This was true regardless of how long or how well stabilized the tuberculosis appeared to be or how minimal in extent at the time of pregnancy. In retrospect, there is no certain way of determining beforehand which tuberculous patient will do well and which one will not, during and following pregnancy except through trial and error; consequently, each succeeding pregnancy is a new problem. Some relatively inactive and apparently healed cases tend to break down under the stress of pregnancy so that the disease may become worse rapidly and endanger the life of the mother. Again, the mother may go through one pregnancy without harm, but break down during another without apparent reason. The risk to the tuberculous mother, therefore, of pregnancy reactivating an apparently inactive tuberculous lesion not controlled with collapse therapy is real and must be taken into consideration in advising pregnancy. Reactivation of mild inactive tuberculosis not treated with pneumothorax may be expected in approximately 30

per cent of cases, and in about half of this number, collapse therapy may actually be necessary to bring the reactivated tuberculosis under control. Obviously, the more extensive the disease and the less stabilized, the greater the risk. In this respect, it is worth recalling that Norris and Landis[1] in a study of 103 pregnant women made at the Phipps Institute and the University of Pennsylvania Hospital in 1918, in the days when little or no collapse therapy was used and routine x-ray studies of the chest were uncommon, found that about 20 per cent of mild, quiescent cases and 70 per cent of more advanced cases exhibited exacerbations during pregnancy or the puerperium.

Summary and Conclusions

This presentation concerns itself with the immediate and late effects of pregnancy, and the responsibilities which follow, upon advanced tuberculosis in a single series of twenty-six white women who were treated with collapse therapy to control the tuberculosis before giving birth to one or more children. These women were of about the same social and economic status and have been under constant clinical and roentgenologic observation for varying periods during the past fifteen years. The average for the group was approximately nine years.

These twenty-six women had forty-eight known pregnancies following collapse therapy and gave birth to forty children, of whom thirty-six are alive and well. Fifteen women gave birth to one child, nine to two children, one to three children (one set of twins), and one to four children.

While the number of cases reported is too small to warrant definite and final conclusions, this study does point to certain facts:

1. Pregnancy, and the responsibilities which follow, can and do affect some patients with tuberculosis unfavorably; therefore, childbearing should be looked upon as a potential hazard for a tuberculous mother. Exacerbation may occur either in the early months of pregnancy or within the first few months following delivery.

2. Collapse therapy has definitely minimized this risk and has brought a better outlook to the expectant tuberculous mother. It has restored to her the right of motherhood. Each case, however, must be carefully evaluated on its own merits, including physiologic and social factors, as well as pathologic, before deciding for or against pregnancy.

3. If the disease, though advanced, is limited to one lung, as indicated by x-ray, and the diseased area is anatomically well collapsed with all cavities closed, the sputum free of tubercle bacilli, and the collapse maintained throughout pregnancy, there is little or no risk of reactivating the tuberculosis and such women may safely undertake one or more pregnancies. The same is true if there is advanced tuberculosis in both lungs, but with the disease in each lung controlled with adequate collapse therapy. Indeed, one may regard the interval of effective collapse therapy as the safest period for a tuberculous woman to marry, have children, and rear a family.

4. If there is disease in both lungs and only one lung, the "worse" lung, is treated with localized collapse therapy, the disease in the uncollapsed lung, although quiescent before pregnancy, may become active in approximately 30 per cent of cases. In about half of this number, collapse therapy may actually be essential to control the reactivated disease in the untreated or contralateral lung. This is true even if the disease in the contralateral lung is minimal in extent, well stabilized for months or years, and the sputum negative for tubercle bacilli at the time of pregnancy. The risk, of course, is greater when the disease is more advanced and less stabilized.

5. The possibility of reactivating quiescent tuberculosis in an uncollapsed lung, however, is not in itself a contraindication to pregnancy. Permission may be given as long as the patient is kept under observation and is willing to accept collapse therapy when it first becomes indicated. Such women may assume the added hazard of pregnancy to their tuberculosis with the assurance that effective help is available when needed.

6. Pneumothorax therapy may be considered as an alternative to therapeutic abortion in the presence of active tuberculosis first recognized during the early months of pregnancy. When the collapse is good and promptly controls the tuberculosis, the woman may proceed safely to term.

7. Only collapse therapy which produces adequate localized collapse of the diseased portion of the lung, such as pneumothorax, maintenance oleothorax, or thoracoplasty, will prevent reactivation of the disease. Indirect collapse, such as phrenic nerve interruption, is not enough.

8. Inadequate collapse therapy—that is, inability to close cavities and render positive sputum free of tubercle bacilli—may be considered the same as if no collapse therapy is employed so far as the effect of pregnancy on the tuberculosis is concerned. The majority of such patients with advanced disease do poorly and pregnancy is inadvisable.

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2109 SPRUCE STREET

THE CONSTITUTIONAL TYPE OF FEMALE PRECOCIOUS PUBERTY WITH A REPORT OF 9 CASES

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PRECOCIOUS puberty is generally looked upon as due to an endocrinopathy of one sort or another, and most often to a tumor of one of the ductless glands. When it occurs in the female suspicion is likely to turn first to the ovary, because of the fact that granulosa cell tumors of this organ have been shown to be capable of producing the syndrome of premature puberty when they arise in early life. There can be no criticism of alertness to this possibility, but it should be borne in mind that, while granulosa cell tumors are no longer looked upon as rare, they are certainly far more infrequent in young children than they are during and after reproductive life. As a matter of fact, in the most recent review of the subject (1941) Lull[1] was able to collect from the literature only 16 cases in which granulosa cell tumors had been found responsible for premature puberty.

One of the purposes of this paper, as a matter of fact, is to emphasize that this granulosa cell tumor type of sex precocity is really much less frequent than certain others. Emphasis on this point is not purely academic. In the days of our early lively interest in the then newly recognized granulosa cell type of tumor, some of us, including myself, were wont to assume the probable existence of such growths when confronted with cases of female sex precocity, even when no tumor could be clearly demonstrated by palpation. Knowing that even small endocrine growths can produce profound biological effects, exploratory laparotomy has often been done in the hope of revealing small neoplasms in the ovary. In the majority of such cases no tumor will be found, and, to anticipate, one of the conclusions of this paper will be that if careful pelvic examination under anesthesia reveals no suggestion of ovarian enlargement or tumor, there is no indication for exploratory operation. I shall, however, return to this point later.

Causes of Female Precocious Puberty

As regards sex precocity in general, the endocrine tumors which may be responsible have been considered to be those of the adrenal, the pineal body and the gonads. It is curious that, in spite of the dominating role of the pituitary in the endocrine mechanism of reproduction, there is no reported instance of a pituitary tumor in association with precocious puberty.

Adrenal Tumors

There is ample evidence that tumors of the adrenal body can produce precocious puberty in either sex, more often in females than in males. This variety, however, will rarely be encountered in gynecologic practice. Its clinical features are such that it will not often be confused with the syndrome evoked by granulosa cell tumors. Precocious menstruation, for example, is an unusual feature, having been observed in only 4 of the 40 cases of adrenal type collected by Reilly, Lisser and Hinman.[2] The premature developmental changes are of dominantly heterosexual character, with hirsutism, hypertrophy of the clitoris and in some cases the pronounced muscular development which brings about the so-called "infant Hercules" appearance. In a minority of cases obesity may be a pronounced feature of the syndrome. The degree of heterosexual development depends upon the age at which the cortical lesion develops. In the congenital or fetal group, actual pseudohermaphroditism may be produced. When the lesion develops in early childhood, with which phase we are more particularly concerned in this paper, the syndrome of macrogenitosomia results, characterized by the symptoms already mentioned. In adults varying degrees of the so-called virilismus are brought about.

On the whole, the effects of such lesions are masculinizing or virilizing, in contrast to the purely feminizing or prefeminizing effects of granulosal or thecal tumors of the ovary. This distinction is well shown in the hypertrichosis which is a part of both syndromes. With ovarian feminizing tumors the hair growth is seen only on the genitalia and in the axillae, where it occurs normally at puberty. With adrenal macrogenitosomia, on the other hand, it involves also other parts of the body, such as the face, back, abdomen and extremities.

Pineal Tumors

The role of pineal tumors, especially teratomata, in the production of premature sex development, appears to be attested by the report of a considerable group of cases of such an association. Bing, Globus and Simon[3] were able in 1938 to collect from the literature 177 such cases. The fact that only 1 of these was in a female justifies the statement that this variety is of little practical significance in gynecologic practice. Furthermore, the syndrome produced by such lesions, macrogenitosomia pinealis, is apparently quite similar to the macrogenitosomia of adrenal cortical tumors. Finally, evidence is accumulating to the effect that the sex manifestations of pineal tumors are merely the results of pressure upon certain brain areas in the floor of the third ventricle or hypothalamus, and not to any endocrine effect emanating from the pineal body itself.

Ovarian Tumors

As to the role of ovarian tumors, those of granulosal and thecal type, there is of course no doubt that these, when they arise in early life, do bring about precocious puberty, and a true puberty in the sense that, with one important exception, the phenomena produced are like those normally seen at puberty. The exception to which I refer is that ovulation is lacking, the menstrual periods being of the anovulatory, estrogen-induced type. This is in sharp contrast to the "constitutional" group of cases with which this paper is chiefly concerned, as I shall later emphasize.

I have already referred to the rarity with which ovarian tumors are found to be responsible for premature puberty. Only one case has been encountered in the department of gynecology among the more than 60,000 patients who have been treated in the past 60 years. This case I reported in 1933,[4] together with two others from which tissue had been sent to our laboratory for study from other institutions. At that time there had been reported only 3 other instances of this type, and in all the years since then the total number in the literature of the world has risen to only sixteen.[1] I mention this to emphasize again that, interesting and important as this type of precocious puberty is, I believe it to be much less common than the non-neoplastic variety which will be presently described.

Cerebral Type

A considerable number of cases have been described in which precocious puberty has been produced by lesions involving various portions of the brain, and especially the region of the hypothalamus and the floor of the third ventricle. It has already been mentioned that pineal tumors probably bring about precocious sex changes through pressure effects upon the above-mentioned brain areas, and it is quite possible that a similar mediation explains sex precocity produced by encephalitis, tumors of the tuber cinereum and mammillary bodies, hydrocephalus and various other brain lesions which have apparently brought about precocious sex phenomena. Even the case reported by Ford and Guild,[5] of precocious phenomena due to postmeasles encephalomyelitis, may be explained by some such mechanism.

As for actual tumors of the hypothalamus, Weinberger and Grant[6] have collected 15 cases in which such growths, with no involvement of the pineal, had brought about precocious sex development. On the other hand, many cases of pineal tumor have been noted in which no sex changes had been observed. These authors have brought together a considerable array of both clinical and experimental evidence concerning the functional interrelationship of the hypothalamus and the hypophysis. There is as yet no certainty as to the exact mechanisms involved, but the concept of Bing, Globus and Simon[3] has the ring of plausibility. These authors believe that, while the pituitary dysfunction is directly responsible for the sex phenomena, it in turn is caused by disturbances in the innervation from the hypothalamic areas as a result of lesions involving that region.

Finally, it is probably in this cerebral group that we can, tentatively at least, place the so-called Albright syndrome, described first by Albright, Butler, Hampton and Smith in 1937.[7] This may occur in either males or females, but apparently only in the latter is premature sex precocity observed. However, the sex changes are overshadowed by the other phenomena of the syndrome, which consist of widespread skeletal changes in the form of osteitis fibrosa disseminata and often bone cysts, together with cutaneous pigmentation. While instances of Albright's syndrome are being reported with increasing frequency, it will scarcely be encountered in gynecologic practice, and it is mentioned here merely for the sake of completeness.

Constitutional Type of Precocious Puberty

There is one other type of precocious puberty which I believe to be the most common of all, but it has received the least attention in the literature. This is probably due to the fact that it occurs in the absence of any tangible or demonstrable cause, while with the others a definite etiologic factor, such as a tumor of one of the endocrine glands, can be discussed as the probable or undoubted cause of the syndrome. In cases of what may be called the constitutional group, however, no such factor is demonstrable, nor does the subsequent course of the patient suggest that such a factor may have existed and been overlooked. Patients of this group simply develop perfectly normal puberal phenomena at an abnormally early age, appearing to skip all or part of their childhood, and at times jumping from infancy to puberty.

The classical work of Smith and Engle, paralleling that of Zondek and Aschheim, has established beyond doubt that the motivation of puberal functional activity in the ovaries is evoked by the underlying gonadotropic activity of the anterior pituitary. This would at once suggest that in these cases of precocious puberty in which no lesion of any other endocrine gland ever materializes there might be present in the anterior pituitary an adenoma, perhaps of very small, subclinical size, and that this might bring about the syndrome, much as a tiny basophilic adenoma can produce the profound biological changes characterizing the Cushing syndrome. However, it is a remarkable fact, as already mentioned, that in not a single reported case of precocious puberty has a tumor of the pituitary been demonstrated. On the other hand, tumors of glands which may be considered to be of only auxiliary sex importance as compared to the pituitary, have been frequently reported.

What, after all, is the biological significance of normal puberty? The easy explanation which we so complacently set forth is that the responsible factor is the ovarian estrogenic activity which begins at a certain age, producing characteristic physiological and anatomical changes in certain tissues and organs. Two factors are thus essential to the production of the puberal phenomena, viz., the ovarian hormone and the selective responsiveness of certain body tissues and organs. But why do these factors so inexorably go into conjunction at a characteristic age of 13½ or 14 years, with usually only minor individual variations in either direction? Certainly this is not to be explained by absence of sensitivity in the recipient organs and tissues before this age, for even in the infant and very immature girl estrogen stimulation can bring about puberal changes, as is well illustrated by the effects of granulosa cell tumors at this age.

And how are we to explain the selective effect of these hormones upon certain tissues, often far removed from one another, such as the genitalia, the breast, the axillae and the larynx, except on the basis

of an underlying foreordained sex pattern innate in the human mechanism, and having its source in the chromosomes themselves? To try to explain all of the normal sex phenomena or their many abnormalities on a purely endocrine basis is superficial and wrong. While the immediate motivating force in the reproductive physiology is the endocrine system, primarily the ovaries and the hypophysis, there is no evidence that it plays an important part in certain more fundamental aspects of sex differentiation. We know very little as yet as to how these two forces interdigitate and how they supplement each other.

No other explanation seems possible than that the underlying factor which normally brings about the characteristic development of puberal changes at a certain age period emanates from certain genes, though we know almost nothing as to the mechanism involved. Puberty may be advanced or it may be retarded by endocrinopathies of one sort or another. On the other hand, it may be advanced or retarded also as a result of an abnormal genic factor. In the case of precocious puberty, therefore, such a genic abnormality may set the characteristic female endocrine mechanism into motion at an abnormally early age. This concept would seem no less rational than the commonly accepted explanation of hemophilia as due to an abnormal gene of recessive type in the sex chromosome. Bauer[8] has developed very elaborately this thesis of the probable constitutional or genic nature of various diseases, including some which parade clinically as endocrinopathies, and are commonly so considered and treated.

Whether or not this concept is correct, certainly there is no evidence in the cases of precocious puberty which are discussed in this paper of any purely endocrine factor, neoplastic or otherwise, nor do they come into any of the other categories which have been enumerated. They are all characterized by the development in otherwise normal children of puberal changes which are entirely normal except for the age at which they appear, and their later course reveals no other abnormality. Such patients simply skip from infancy or early childhood to puberty. In so far as our present knowledge is concerned, the designation of constitutional appears to be justified for this type of precocious puberty.

Incidence of Constitutional Type

As to the incidence of the constitutional type of sex precocity I do not believe that any intelligent estimate can be derived from a study of the literature. Not only must many cases go unrecorded, but others have been reported simply as instances of precocious puberty of obscure or uncertain causation, or have been buried in the reports of series of cases of all sorts of etiological types. This is true of even such exhaustive reports as those of Reuben and Manning,[11] Neurath[9] and Lenz.[10] For example, in the collective review of 130 cases made by Lenz in 1913, it is quite clear that in addition to his own patient,

several others in his series are of constitutional type. The case of Robbelin, in which menstruation appeared at 6½ years, was followed for 26 years, during which time she remained well and menstruated normally. Such a history would appear to exclude neoplastic disease, especially as most of the reported cases of adrenal, pineal or hypothalamic type have succumbed within a comparatively short time. Lenz's own patient, in whom menstruation began at four, was observed until the age of 14, when she was still entirely well and menstruating normally. One of my own cases (Case 1) was observed from the age of 16 months to 10 years, during which she remained well except for her regular menstruation and other puberal characteristics. A review of many other cases reported in the literature as of obscure causation leads me to the conclusion that they belonged to this group (Elterich,[12] Fischer,[13] Craven,[14] Mengert,[15] etc.). For reasons which I shall elaborate later it seems certain that in this category we must also place the remarkable cases of abnormally early pregnancy which have been reported from time to time.

If my own experience with this variety of precocious puberty could be taken as an index of its comparative incidence (I appreciate the fact that it cannot) it would seem far more frequent than the only other variety with which it is likely to be confused, or which is apt to be encountered by the gynecologist, i.e., the granulosa cell ovarian tumor group. While I have reported 3 cases of the latter group, none has occurred in my own practice, and only 1 of the three was encountered in the gynecologic department of the Johns Hopkins Hospital. On the other hand, I am reporting today 9 cases of the constitutional type, and 6 of these were observed in my own private practice. Two of the remaining cases were encountered in the Harriet Lane Home for Children of the Johns Hopkins Hospital, and for permission to add these to my own I am indebted to Dr. Edwards A. Park, the director of the Harriet Lane Home. One case was from the practice of Dr. Thomas K. Galvin, who kindly sent me sections of the ovarian biopsy and permitted me to include the case in this series.

Clinical Characteristics of Constitutional Variety

According to most authors puberty should be considered abnormally early or precocious when it occurs below the age of 9, although some suggest a lower limit of 8. I need not here elaborate on the obvious distinction between puberty and the menarche, or stress the fact that the first menstruation is only one of the developmental phenomena which characterize puberty. It is only natural, however, that the first menstruation, constituting as it does the most conspicuous phenomenon of puberty, has in the literature been utilized as the most convenient chronological marker for the puberal epoch. I may add that the ages of the 9 patients reported in this paper were well below even the arbitrarily set minimum of 8 years. A number of additional cases in

which the age was within a year or so of this limit has been excluded from the report. The age at which the first menstruation occurred in the 9 patients of my series was as follows: 15 months, 2; 2 years 8 months, 4; 4½, 6½, 7 (2 cases), 7½.

Not much need be said about the clinical characteristics of this type of precocious puberty, as they are apparently exactly those seen with normal puberty except for the age at which they appear. These precocious children are apt at first to be taller than normal for their age, but their later growth is likely to be inhibited and they might then be shorter than the average. Lenz's patient, for example, was for some years taller than her 2 year older sister, but at 14, the latter had outstripped her in height. For a full discussion of the skeletal growth changes in cases of precocious puberty the reader may be referred to Lenz's paper.[10]

There are, so far as I know, practically no available data as to the age at which the menopause occurs in these patients, although it seems likely that the climacteric epoch is not notably accelerated. This would seem to be indicated by the fact that Robbelin's case[10] was still menstruating normally at 32½ years, and that Haller's patient,[10] in whom menstruation appeared at 2½ years, had her menopause at 52. So far as I can find there is available in the literature no report of autopsy in any patient who had passed through this form of sex precocity, and it is probable that the post-mortem study of the endocrine glands would not be especially revealing.

The clinical feature of these cases which distinguishes them from the granulosa cell group, and which has apparently received no previous emphasis, is that *in the constitutional group the patients not only menstruate unusually early, but they also ovulate.* By contrast, the granulosa cell patients menstruate but they do not ovulate. The periodic bleeding in the latter group is, in other words, of the purely estrogen-induced type. In the constitutional group, on the other hand, the full puberal mechanism is evoked, with both menstruation and ovulation. That this is so is indicated by the fact that in 3 of my cases in which exploratory operation was done biopsy of the ovaries revealed indubitable evidence of preceding ovulation in the form of corpora lutea at various phases (Cases 1, 2 and 4).

The practical significance of this observation is that in certain cases of the constitutional variety pregnancy is possible if insemination occurs, while this is not true of the granulosa cell tumor group. As a matter of fact, it seems certain that all of the cases of abnormally early pregnancy which have been reported must have been cases of the constitutional puberal variety, in which both menstruation and ovulation had been evoked at abnormally early ages. The recent much publicized case of Lina Medina, the Peruvian child who gave birth to

a child at the age of 5 years and 8 months, making her the youngest mother in the world's history, undoubtedly belongs to this category. According to Escomel's report of this case,[16] menstruation had begun at 7½ months and continued until impregnation. At the time of her cesarean section biopsies of the ovary were made, showing an adult type of ovarian tissue and also the corpus luteum of pregnancy. The much quoted case of Anna Mummenthaler, reported in 1751 by Haller,[17] concerned a patient in whom menstruation appeared at 2, with the first childbirth at 9. Another well-known case, also in the very old literature, is that of Mandeslo,[10] in whom a child was born to a girl of 6, in whom menstruation had occurred at 3. In the case of precocious puberty reported by Chaschinsky and Jershow in 1933,[17] full-term pregnancy occurred at the age of six. A goodly group of other cases of abnormally early pregnancy have been reported, and no explanation seems possible except that they represented instances of constitutional precocious puberty.

As with normal puberty, ovulation is not necessarily inaugurated when menstruation begins. It is highly probable that in children exhibiting this form of precocious puberty the early cycles are not infrequently anovulatory, and this would seem to be at least suggested by the operative and biopsy findings in one of my cases (Case 9). Data on this point are too meager to justify any generalizations. Moreover, as with normal puberty, the rhythm of menstruation is not necessarily regular in these precocious cases, and periods of amenorrhea may be noted, as in my Case 5.

Management

There are two points of obvious importance in the management of these patients which deserve emphasis. The first pertains to the psychologic management of the patient and her family, especially the mother. The latter is quite sure to be distressed by the abnormally early appearance of menstruation and other sex manifestations in the child. The situation should be explained to her as fully and fairly as possible, with reassurance as to the essential harmlessness of the condition in itself. She should be told that the precocious manifestations will persist, but that after the age of about 9 or 10 the child will not be different from many other girls of her age. It is inevitable that in the earlier years of childhood the sexually precocious girl will be conscious of the differences between herself and others of her age, and one can understand the self-consciousness and morbidity which this is likely to engender. An understanding and sympathetic mother can render her child a great service by her guidance and protection through these trying years.

The second point to stress is that since ovulation may undoubtedly occur in girls with this type of precocious puberty, they must be care-

fully guarded against sex violations, which might result in impregnations. One naturally hesitates to question children on the subject of possible sex attractions, but in at least one of my cases the mother volunteered the information that the child was "very fond of the boys." It is easy to understand that the reverse might also be true, in view of the physical attractiveness of some of these young patients.

Fig. 1.—Case 1. Age 16 months. First menstruation at 15 months. Patient entirely well and menstruating normally at age of 10 years.

Case Reports

Case 1.—R. R., aged 15 months, was first seen at the Harriet Lane Home, Johns Hopkins Hospital, in April, 1932, in consultation with Dr. Edwards A. Park, who later kindly referred her to me for further management. When the child was 6 months old, the mother noticed a white vaginal discharge, which recurred again one month later, and again three months thereafter. At this time enlargement of the breasts was first noted. After this the vaginal discharge persisted, but repeated examinations revealed no evidence of gonococcal infection. There was no further medical examination until the child, at 15 months, was brought to the Johns Hopkins Hospital for treatment. At this time there was a fairly profuse whitish discharge, which on smear showed many large epithelial cells and no pus cells. Bacteriologic examination showed only a mixed flora of gram-positive organisms. A few days later the child had a profuse menstrual bleeding lasting 2 days, with staining for 2 additional days. She was then admitted for further study.

The child (Fig. 1) was then a rather pretty, intelligent Jewish girl of 15 months, slightly taller than the average for her age, her height being 85 cm. and weight 9,850 Gm. Both breasts were moderately enlarged. The genitalia showed a moderate growth of dark hair, and there was a similar growth in the axillae. Both the labia majora and minora were well developed, and the uterus, on rectal examination, was almost 5 cm. in length. Both ovaries were definitely larger than those of a normal child, the right being distinctly larger than the left. Hormone examinations of the urine were made by Dr. R. T. Frank, who reported approximately 40 mouse units of estrogen with small amounts of gonadotropic hormone. X-ray study showed bone development to correspond to her age, with a normal sella turcica. Numerous other studies, including a ventriculogram, were made with essentially negative results. The child was then discharged and referred to me by Dr. Park for further management.

When seen again on November 17, 1932, the puberal changes had become more fully developed. Her height had increased to 38¼ inches (97 cm.) and she weighed 25 pounds. Menstruation had continued to recur at approximately monthly intervals, and the pelvic examination showed the right ovary still distinctly larger than the left, so that the possibility of a small granulosa cell tumor could not be eliminated, and the child was admitted to my service at Bon Secours Hospital for exploratory operation.

The laparotomy showed the pelvic organs to be of essentially normal puberal appearance. The uterus was 5½ cm. in length, with a full and rounded fundus. The left ovary measured 2 by 1 by 1 cm. but the right was considerably larger, measuring 2½ by 1½ by 1½ cm. with slight lobulation apparently due to the presence of cystic follicles beneath the surface. One surface follicle measured 1 cm. in diameter. No neoplasm could be felt in either ovary, and an incision into the right ovary disclosed none. A yellowish body, evidently a retrogressed corpus luteum, was encountered just beneath the surface and a biopsy was made in this area (Fig. 2). The microscopic examination confirmed the nature of the retrogressed corpus luteum. The adrenals were normal in size.

Since this operation the patient has returned to Baltimore for examination on a number of occasions. She has been entirely well and has

been menstruating normally and without pain. No sign of any granulosal or other endocrine tumor has ever developed. The last examination was made 2 years ago, after which her mother moved to another city, and it has not been possible to trace her.

Case 2.—E. M., aged 9, was referred to me on April 28th, 1938, by Dr. James Taylor, of Altoona, Pa. At the age of 6 the breasts began to grow large and full, with rounding of the figure and the appearance of axillary and pubic hair. Her general appearance, when first seen, was that of a girl of about 13 or 14 (Fig. 3). Her height was 54¼ inches, and her weight 90 pounds. She was bright and vivacious, and her school work was described by her mother as of average grade. The first menstruation occurred at 7½ years, with intervals for a time of 28 days, but more recently 19 or 20 days, the amount being quite profuse.

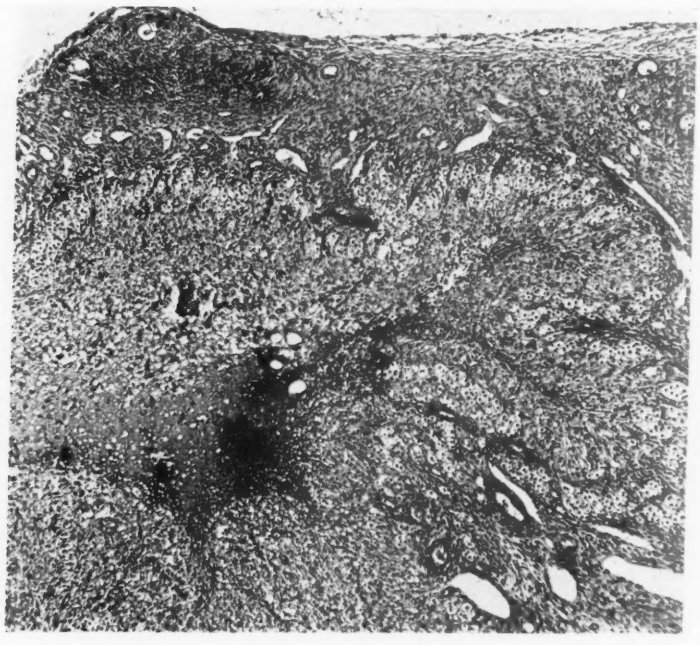

Fig. 2.—Typical corpus luteum in slightly retrogressive phase in ovary of Case 1.

The genital findings need not be described in detail, since they were those characteristic of the normal girl of puberal age. The left ovary was enlarged to about the size of a walnut, so that a small granulosal growth could not be excluded. Routine laboratory studies yielded normal findings. Estrogen determinations by Dr. Brack showed a hormone content only slightly lower than that of the average puberal girl. X-ray studies showed epiphyseal closure not yet complete, and the sella was normal. Neurologic studies were negative. Because of the enlargement of the left ovary, and the possibility of a small granulosal tumor, an exploratory laparotomy was thought advisable.

Operation revealed pelvic organs of puberal degree of development. The slight enlargement of the left ovary was due to a small follicle cyst. A yellowish body was noted just beneath the surface of the left ovary, and a biopsy at this point confirmed the presence of the corpus luteum shown in Fig. 4.

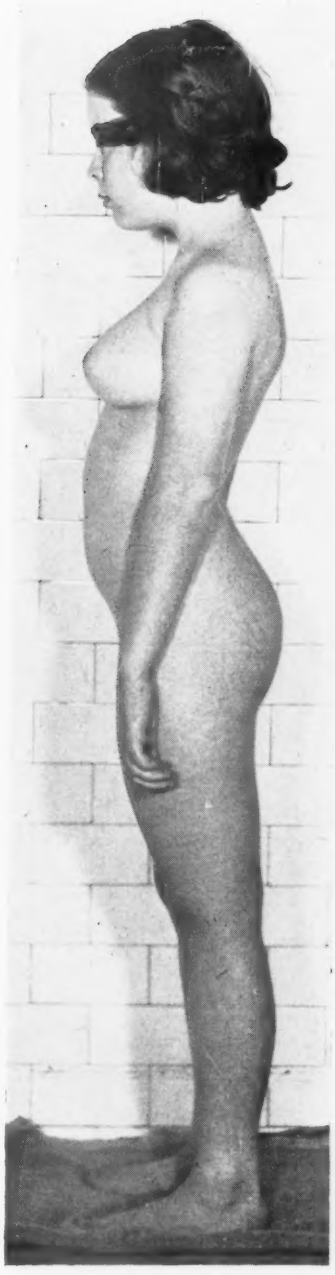

Fig. 3.—Case 2. Age 9 years, but menstruating normally since age of 7½.

An examination of this child 1 year after operation showed no suggestion of ovarian neoplasm, and a very recent report from the mother states that she is quite well, with normal menstruation.

Case 3.—S. H., aged 9 years, was referred to me on February 27th, 1938, by Dr. E. W. Johnson of Baltimore. Since the age of 6½ she had menstruated at about 4 weekly intervals, the flow lasting 5 days, moderately free, with no pain. At approximately the time of the menarche the breasts began to enlarge and hair appeared in the axillae and on the genitals. The breasts since then have become quite large, and she now has the appearance of a girl of 14 or 15 (Fig. 5). The pelvic examination showed the uterus to be of normal puberal size, and the ovaries were likewise much larger than that of a normal child of her age, the left

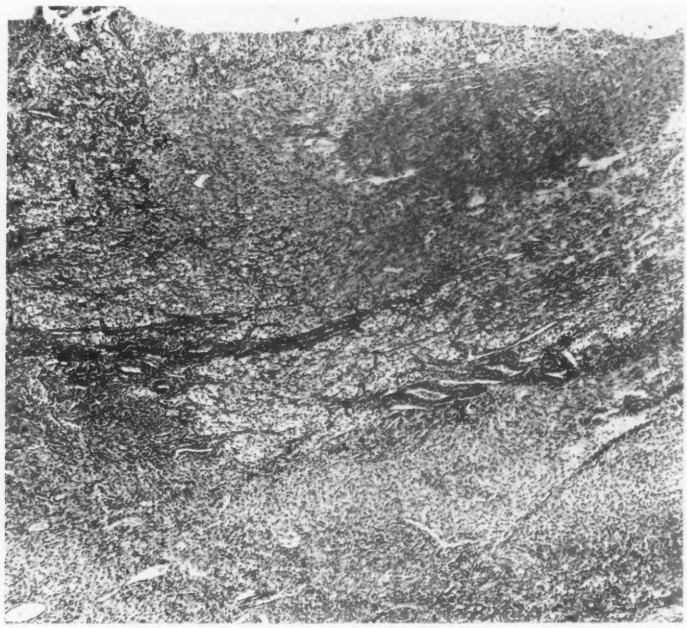

Fig. 4.—Corpus luteum from ovary of Case 2.

being larger than the right. The urinary hormone study, made by Dr. C. B. Brack, showed an output of more than 3.3 and less than 4.4 R. U. per liter. Other laboratory studies were negative, and will not be detailed. Because of the left ovarian enlargement exploratory laparotomy was done, but it showed no granulosal tumor. The ovarian enlargement was due to the presence of a small follicle cyst. There was no gross evidence of corpora lutea. A biopsy of the left ovary was done, showing follicles in various stages of maturation, but no evidence of corpora lutea, though the examination of one small bit of ovarian tissue could not of course exclude the presence of lutein tissue elsewhere.

Case 4.—L. F., aged 10, was referred to me by Dr. Gabriel Pickar, of New Brunswick, N. J., on January 17th, 1941. She had begun to menstruate at the age of 4, and at about the same time the breasts exhibited marked hypertrophy, with soon an abundant growth of axillary

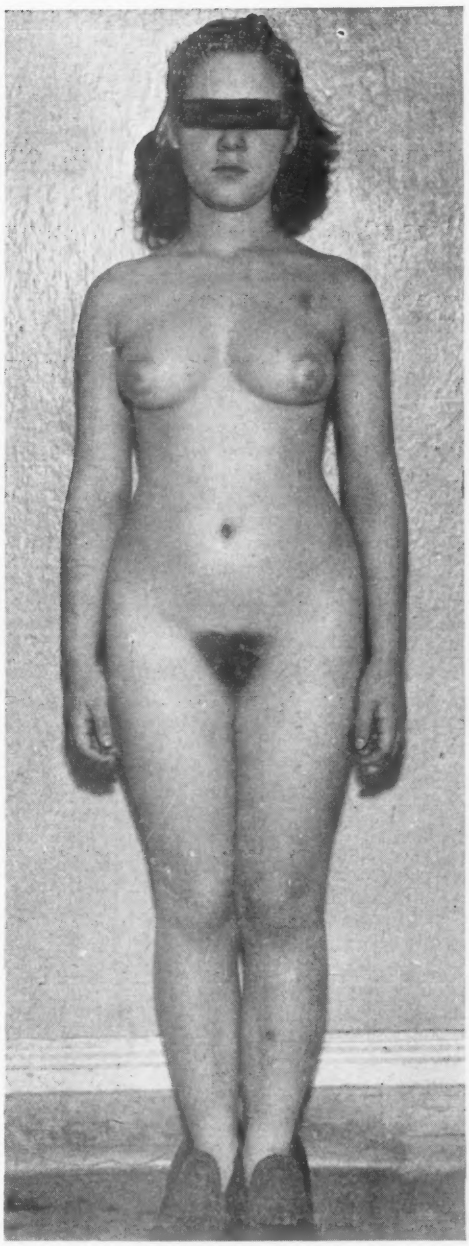

Fig. 5.—Case 3. Age 9 years, but menstruating regularly since the age of 6½.

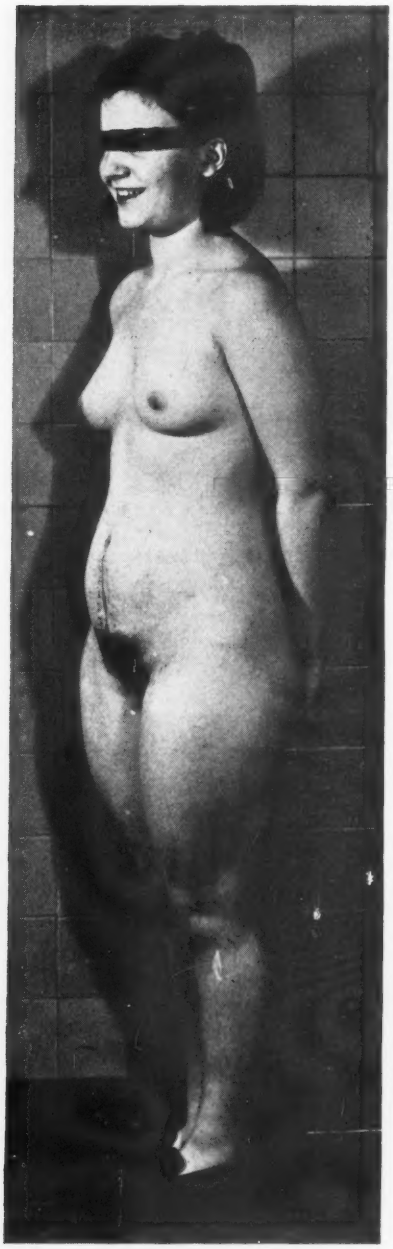

Fig. 6.—Case 4. Age 10 years, but menstruating normally since age of 4.

and genital hair. The periods have since then occurred at regular intervals of about 4 weeks, and the figure has become full and rounded. (Fig. 6.) She is of normal intelligence for her age, and is described by her mother as rather "fond" of the boys. At the age of 5 the patient was operated upon at a hospital in Trenton with a preoperative diagnosis of granulosa cell tumor, and the left tube and ovary were removed. There was, however, no recession of the precocious sex changes. An effort was made to secure tissue or slides, but this was unsuccessful. Some time later, however, Dr. Pickar was able to ascertain that the pathologist's report indicated no evidence of tumor, the sections showing what he interpreted as normal adult ovarian tissue.

Following the operation the patient developed considerable pain in the left lower quadrant, and as there was still a clinical suspicion of granulosal tumor, the patient was referred to me for treatment. She was then 10 years of age.

Her general appearance, as will be seen from her photograph (Fig. 6), was that of a girl of perhaps 14 or 15 and, without going into detail, the generative organs likewise corresponded to that age. Her height was 55¾ inches, and her weight 105 pounds. Routine laboratory studies showed normal findings, as did the neurologic examination. X-ray studies of the bones showed the epiphyses already closed. The sella was normal. Basal metabolic rate was minus 21 per cent. Estrogen urinary studies by Dr. Georgeanna Seegar-Jones showed an output of between 20 and 25 rat units.

The pelvic examination made per rectum showed the uterus to be of about the average nulliparous adult size. The right ovary likewise was well developed. There was extreme tenderness in the left side, with some thickening, but no evidence of a tumor of any sort. Because of the patient's constant pain in this region, laparotomy was considered to be advisable.

The operation showed the uterus and right adnexa to be of adult type. The surface of the ovary revealed considerable pitting, indicative of previous ovulations. One or two small cystic follicles were seen on the surface, and also a yellowish body which was evidently a retrogressed corpus luteum. A biopsy was done at this point, and the sections show typical retrogressive lutein cells. (Fig. 7.) The left adnexa had been removed. There were rather extensive and firm adhesions involving the left broad ligament, omentum and several loops of small intestine. These were freely mobilized, with satisfactory peritonealization. Exploration of the abdomen, including the adrenals, showed no sign of any tumor masses. The postoperative course was smooth, and the patient has been free of pain. She has of course continued to menstruate.

Case 5.—B. H., aged 2 years and 8 months, was referred to me on May 17, 1941, by Dr. Robert L. McCrady of Charleston, S. C. She weighed 7 pounds 11 ounces at birth, and had been normal until January, 1941, when her breasts began to enlarge. (Fig. 8.) Several months later a growth of axillary and genital hair appeared, and 10 days previous to my examination, the first menstruation occurred, lasting 2 days. She weighed 33½ pounds and was 36¼ inches in height. A pelvic examination made under anesthesia showed the uterus to be of approximately puberal size, measuring 5 cm. in length. The left ovary was small and beady, the right somewhat larger, but smooth and ovoid.

There was no suggestion of tumor. Other laboratory studies were negative, and the child was discharged, with instructions as to the psychologic management, and as to the importance of periodic examinations.

A letter from her mother on June 17, 1942, reports that menstrual bleeding occurred June 5, June 21, and again July 4, followed by a long period of amenorrhea, with later re-establishment of the flow. Her health otherwise has been excellent.

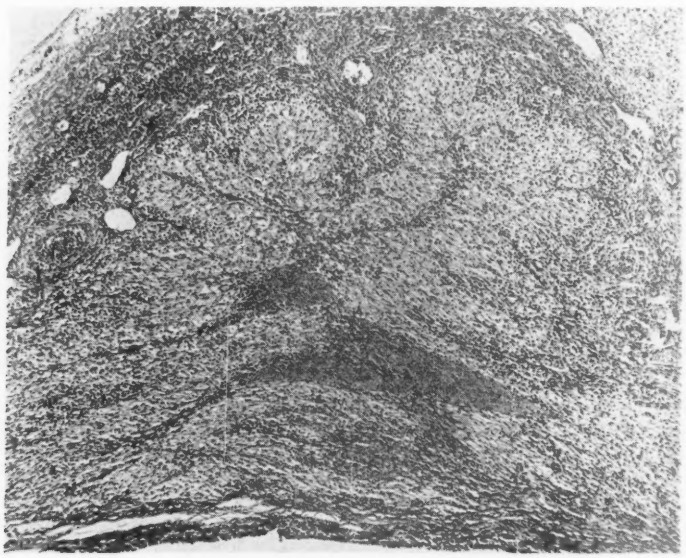

Fig. 7.—Corpus luteum revealed by ovarian biopsy in Case 4.

Case 6.—A. W., aged 6, of Emmitsburg, Md., was seen at Bon Secours Hospital on August 12, 1940. She had entered the hospital for tonsillectomy 2 months previously, and at that time the physical examination showed marked breast development, though she had not menstruated. As her parents, who lived in Emmitsburg, Md., could not then leave her for further study, they were requested to do this later, and she returned in August. At this time she was seen to be tall for her age, her height being 52½ inches. She weighed 63 pounds. The breasts showed striking development. (Fig. 9.) There was only a light beginning growth of axillary and pubic hair. The pelvic examination, without going into details, showed a subpuberal stage of development, with fairly well-developed labia, a uterus which measured approximately 5 cm. in length, and ovaries definitely larger than those of a normal child of 6. There was no palpable suggestion of any ovarian neoplasm. Laboratory studies were essentially negative.

Although the patient had not yet menstruated, it seemed reasonably certain that she would before very long, and this prediction was made and the mother told of the probability. A letter received from her later reported that the first period occurred in April, 1941, eight months after she was seen, at the age of 7. She states that the child has been perfectly well, except for some of the infectious diseases

of childhood, and that she is "extremely bright in her school work and in her music, and she has a wonderful memory."

Case 7.—S. F., aged 7, was admitted to the Harriet Lane Home for Invalid Children on Dec. 20, 1914, because of unusual breast development. (Fig. 10.) Her birth weight was 8 pounds. She was 52½ inches tall, and weighed 68 lbs. The breasts began to develop at the age of 4, becoming quite large in succeeding months. At the time of admission they were described as 16 cm. in diameter, pendulous, with well-marked areolae about the nipples. There was an abundant growth of pubic hair, but none in the axillae. At this time she had not begun to menstruate. Neurologic, x-ray studies and other laboratory studies were essentially negative. The external genitalia were described as much more developed than those of a girl of her age, but unfortunately there is no note as to gynecologic examination.

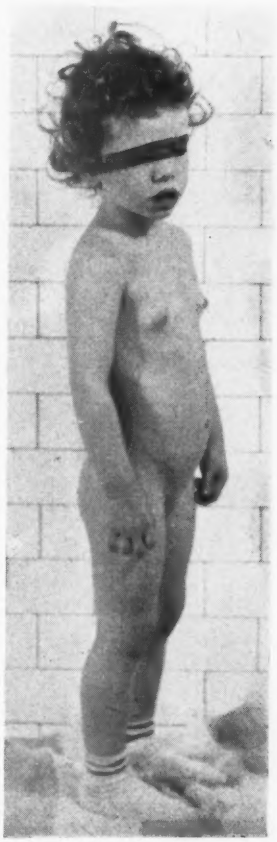

Fig. 8.—Case 5. Age 2 years and 8 months at this time. First menstruation 10 days before this picture was taken.

She remained in the hospital only a few days, but returned to the dispensary on Dec. 31, 1914, when her mother reported that the child had had a bloody vaginal discharge, evidently menstrual. Shortly after this the family moved to parts unknown, so that the efforts of the social service department to get her back for further study were unsuccessful.

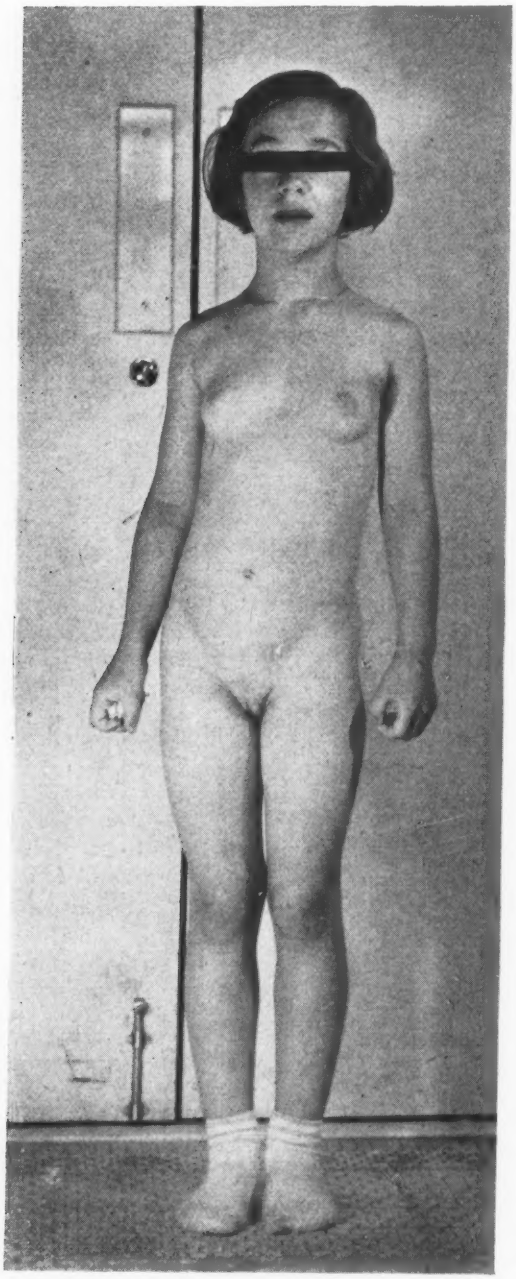

Fig. 9.—Case 6. Age 6 years at this time. Beginning puberal development but no menstruation. Eight months later first period occurred and menstruation has been normal since then.

Case 8.—L. McD., aged 6½, was admitted to the Harriet Lane Home for Invalid Children, Johns Hopkins Hospital, on April 6, 1939. At the age of 2 the mother noticed that the child's breasts were becoming full and rounded, the left more than the right. Some months later a scanty menstrual flow appeared, lasting 1 day. The second flow did not occur until 8 months later, but since then the periods have recurred at intervals of from two to four months, lasting from 1 to 3 days. Axillary and pubic hair appeared within the year following the menarche.

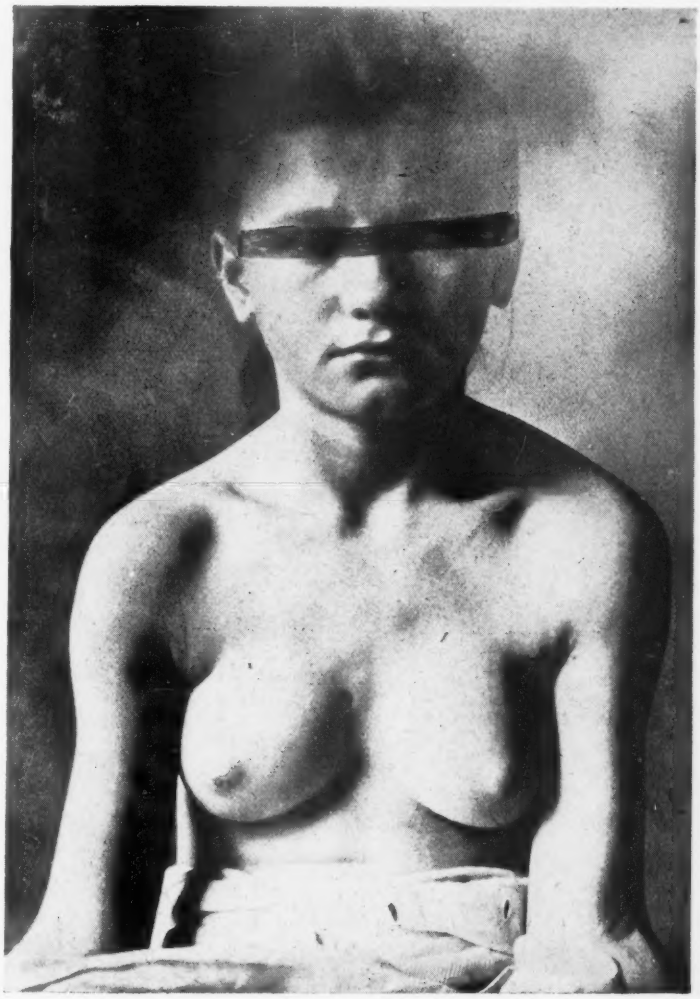

Fig. 10.—Case 7. Age 7 years. First menstruation at this age. (Harriet Lane Home Case.)

The general appearance was described as that of a girl of over 15. The face was rather mature, and the child was cooperative and intelligent. Her height was 52.5 inches. Aside from the physical characteristics above-mentioned, the gynecologic examination showed the external and internal generative organs developed far beyond those of a normal girl of her age, and resembling those of a girl at puberty. There was no

palpable evidence of a tumor. Estrogen urinary titer showed less than 3 R. U. per liter. The bone age corresponded to 12 years. The basal metabolic rate was –4. Other laboratory studies were not significant.

An exploratory laparotomy was done by Dr. R. W. TeLinde, and no evidence of any tumor was found in either ovary, though both ovaries were said to be "more yellow" than the normal adult ovary. No corpus luteum was seen, but a biopsy of the right ovary showed a mature follicle. The uterus measured 6 cm. in length, the ovaries 3 by 1½ by 1 cm.

A report from the mother on Oct. 22. 1940, stated that the child was well, and that menstruation was occurring at monthly intervals, the flow lasting 2 days.

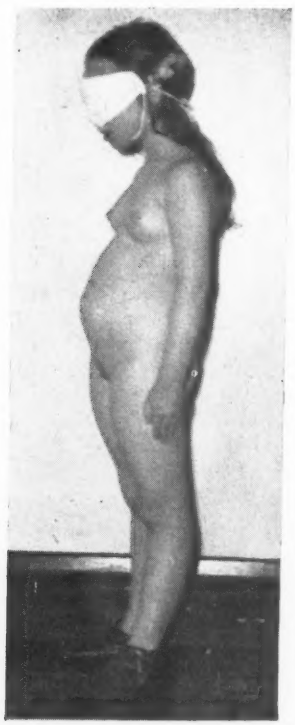

Fig. 11.—Case 9. Age 5 years. First menstruation at 4½. (Case of Dr. T. K. Galvin.)

Case 9.—N. L., aged 5, was admitted on April 20, 1943, to the service of Dr. T. K. Galvin, at St. Joseph's Hospital, and I am indebted to him for permission to include the case with my own group. During the preceding year she had shown increasing development of the breasts, with also development of pubic and axillary hair, and the first menstruation had appeared in November, 1942. the flow lasting 6 days. The periods continued to recur regularly at about four-week intervals. The external genitalia were of normal puberal type. Laboratory studies were essentially negative. As the left ovary appeared somewhat larger than the right an exploratory operation was done by Dr. Galvin, but it revealed no microscopic evidence of granulosa cell tumor. The pelvic

organs at operation "were like those of a girl of 15." The left ovary was removed for microscopic examination. This showed numerous follicles in varying stages of maturation, though no corpora lutea were seen.

Summary

While tumors of certain endocrine glands and various cerebral lesions have been reported often as causes of precocious puberty in the female, there has been little discussion in the literature concerning the constitutional type of this syndrome, probably more frequent than any other. In cases of this sort no tumor or lesion is demonstrable, nor does it manifest itself in the later course of the patient. The clinical characters of the abnormally early puberty are identical with those of normal puberty, except for the age at which they appear. Nine cases of this sort are reported in this paper, the ages of the patient being 15 months, 2, 2 years 8 months, 4, 4½, 6½, 7 (2 cases) and 7½.

As to why an otherwise normal puberal mechanism is awakened at an abnormally early age, no explanation seems plausible except on a chromosomal or genic basis, as is discussed in the paper, so that the designation of "constitutional" seems appropriate for this group.

Certainly cases of this type are far more common than those due to granulosa cell tumors, which gynecologists especially are apt to think of first in association with precocious puberty, often resorting to exploratory laparotomy in such cases. There can be no criticism on this point if there is a suspicious enlargement of the ovary. In the absence of any enlargement it is wiser to refrain from operation, though the patient should be re-examined at periodic intervals.

This study, particularly the microscopic examination of biopsies of the ovaries in several cases, has convinced me that, unlike the granulosa cell tumor cases, those of constitutional type may not only menstruate but also ovulate at abnormally early ages. This would explain the occurrence of pregnancy at extremely early ages, as in the remarkable case reported from Lima, Peru, in 1940, of a full-term pregnancy in a child 5 years and 8 months old.

The most important practical points in the management of these cases are (1) the psychological management, to avoid the development in the child's mind of self-consciousness or a sense of inferiority or abnormality; (2) protection against the possibility of insemination.

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Leffel, James M., Masson, James C., and Dockerty, Malcolm B.: Krukenberg's Tumors, Ann. Surg. **115**: 102, 1942.

The authors discuss the question of what constitutes a Krukenberg tumor? Mucus in the epithelial cells is a constant finding. "Signet-ring cells" are almost a constant finding. They feel that the term Krukenberg's tumor should include all metastatic adenocarcinomas of the ovary.

Four possible routes of metastasis are mentioned. (1) Spread by peritoneal implantation; (2) spread by lymphatic channels; (3) extension by continuity; and (4) spread by way of the blood stream. It is felt that primary adeno-"colloid" carcinoma of the ovary may rarely mimic Krukenberg's tumor. Concerning treatment, the authors feel that if the patient is a poor surgical risk or showing evidence of extensive metastasis, surgical treatment is contraindicated except for the relief of an obstruction of the genitointestinal tract. If a patient is a good surgical risk without extensive carcinomatosis then the uterus, tubes, and ovaries should be removed. An atrophic ovary should never be left intact. It is stated that a good general rule is to remove both ovaries when a solid tumor is found involving either one, particularly if the patient is near or past the menopause.

William Berman

ADRENAL-LIKE OVARIAN TUMOR ASSOCIATED WITH CUSHING'S SYNDROME (SO-CALLED MASCULINOVOBLASTOMA, LUTEOMA, HYPERNEPHROMA, ADRENAL CORTICAL CARCINOMA OF THE OVARY)

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IT IS well known that arrhenoblastomas of the ovary masculinize their hosts. However, it is not generally appreciated that other tumors of the ovary also are capable of producing similar changes in sexual characteristics. Unlike arrhenoblastomas, these tumors are associated with many of the general and metabolic symptoms, such as hypertension, cutaneous striae and diabetes, that characterize Cushing's syndrome, Cushing's disease and tumors of the adrenal cortex.

Cushing's syndrome should be distinguished from Cushing's disease. The term Cushing's syndrome should be applied solely to the now well-known clinical picture described by Cushing. This clinical picture has been found to be associated with basophilic adenomas of the anterior lobe of the pituitary body, adrenal cortical tumors, and adrenal cortical hyperplasia and tumors of thymus associated with adrenal cortical hyperplasia.[12] In all of these conditions Crooke's changes in the basophilic cells of the anterior lobe of the pituitary body have been found to be present.[7] When this clinical picture is found to be associated with a basophilic adenoma of the anterior lobe of the pituitary body, the term Cushing's disease is applicable.

The origin and nature of these tumors are difficult to determine. Their cells resemble both those of the corpus luteum and the adrenal cortex. The clinical symptoms which they produce are strikingly similar to those produced by adrenal cortical tumors and adrenal cortical hyperplasia and consequently are very similar, if not strictly identical, to those produced by basophilic adenomas of the anterior lobe of the pituitary body (Cushing's disease).

It is not surprising, therefore, that pathologists have had difficulty in inventing suitable names by which these neoplasms can be designated. Glynn lumped them into one group to which he referred as "yellow tumors of the ovary." Others, impressed by the histologic similarity of the tumor cells to either the cells of the corpus luteum or to the cells of the adrenal cortex, have introduced such terms as "luteoma,"[21, 27] "luteoblastoma," "hypernephroma" and "adrenal cortical carcinoma" of ovarian origin. The term "luteoma"[28] is particularly unfortunate as it has been applied not only to the group of neoplasms under discussion but also to granulosa cell tumors, the cells of which have undergone

luteinization. Rottino and McGrath tried to escape from the horns of the dilemma by introducing the noncommittal Latin-Greek hybrid "masculinovoblastoma." For various reasons, some of which will be apparent later, none of these designations is satisfactory. Rather than introduce further confusion in nomenclature and yet avoid the difficulties which arise from use of any one term to the exclusion of the others, we have decided to speak of them as "adrenal-like ovarian tumors." To date, thirteen well authenticated cases of such adrenal-like ovarian tumors have been reported in addition to the one which we are reporting. Rakoff[19] also speaks of another case which according to a personal communication will be reported in detail later.

Report of Case

The patient, a white girl aged sixteen years, of Polish parentage, came to the Mayo Clinic August 5, 1942, because of amenorrhea and hirsutism. She was under the care of Dr. L. W. Pollock, with whose cooperation this report is made. One sister was said to have had a similar disorder. As far as could be learned her puberty was normal. The menses began at about the age of eleven and at first were regular and normal. When she was about thirteen years of age the flow became somewhat scanty and sometimes she would skip periods for two or three months at a time. Finally, in October, 1940, at the age of fourteen years, her menses ceased entirely. There were no hot flushes. At the same time coarse, black hair appeared on the face, arms, legs and abdomen so that "hair remover" and finally a razor had to be used. Simultaneously, she gained in weight and her face became full and round. Headaches became very troublesome. By the spring of 1942, her appearance had changed to such an extent that one of her sisters who had been away for some months had difficulty in recognizing her.

Except for a reactive mental depression the girl's psychologic attitude was remarkably good under the circumstances. She made good grades in school, generally a "B" average, and she enjoyed her studies. Specific information regarding her sexual proclivities was difficult to obtain, but her mother stated that she had not noticed anything strikingly abnormal in the girl's behavior toward associates of either sex. She preferred the company of girls and disliked to attend parties and social functions if boys were going to be present. Her relations to the latter were "strictly friendly."

During the course of her illness she had consulted several physicians, and as her condition seemed to be becoming progressively more alarming she decided to come to the clinic.

The patient gave the impression that she was sexually neuter. She objected slightly to being examined, was a bit sullen, but on the whole there was nothing notably abnormal in her behavior in the examining room. She was 5 feet 2 inches (127 cm.) tall and she weighed 141 pounds (64 kg.). Her voice seemed to be somewhat low pitched but the Adam's apple was not abnormally prominent.

When she was undressed, her body conformation and general appearance were distinctly but not entirely masculine in type (Fig. 1). The skeletal framework was heavy and sturdy and the musculature was exceptionally well developed and conspicuous. Her athletic appearance was accentuated by a strong lower jaw, a prominent mental protuber-

ances and a cleft chin. The shoulders were square and broad and the trapezius muscles stood out prominently. The characteristic fat deposits (for example, those above and below the clavicle) which contribute so much to the femininity of the normal woman's appearance were largely, but not entirely, absent. The abdomen protruded and the hips were narrow, especially below the trochanters. A suggestion of a "buffalo hump" was apparent in the cervicothoracic region.

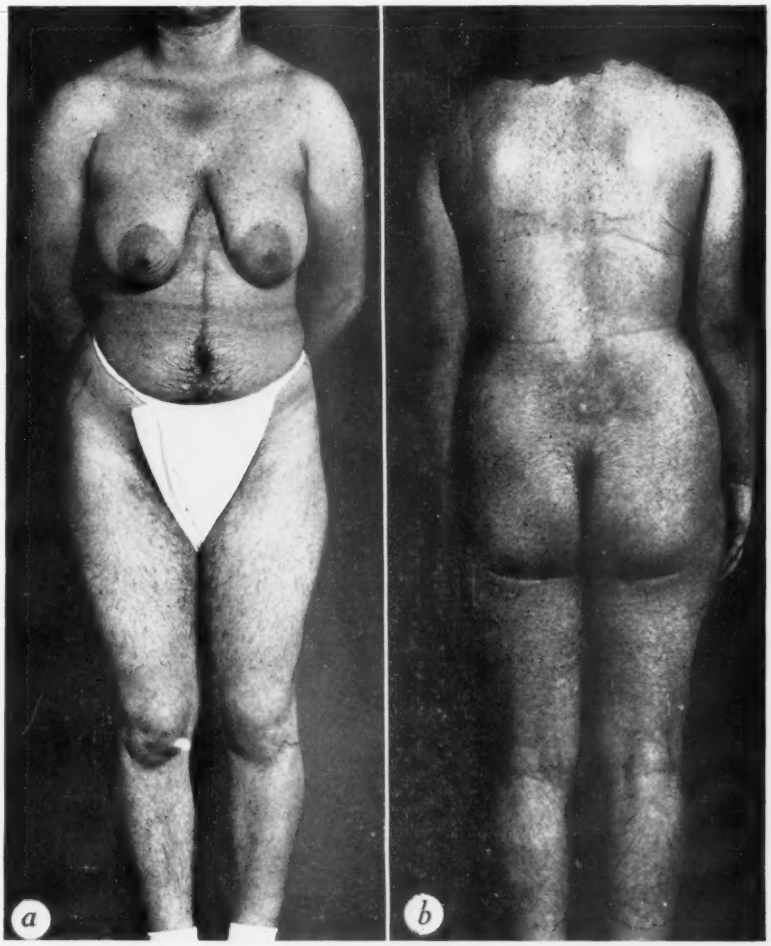

Fig. 1.—Appearance of patient's body before operation.

Her face (Fig. 2) was slightly rounded; the palpebral fissures were narrowed because of drooping upper lids and the corners of the mouth were depressed. All of these factors contributed to give her a "down-at-the-mouth" look. The skin was dry and rough because of extensive areas of keratosis pilaris, and between the shoulders and down the back there was a well-marked acneform eruption. Below the iliac crests there were well-defined purplish striations. In color, the skin was somewhat florid and this was especially noticeable in the face. On the arms, legs, thorax and abdomen, back and buttocks there was a prominent overgrowth of coarse dark hair. At the temples the hair of the scalp was

beginning to recede, side burns extended down the cheeks, and the eyebrows met at the midline. Curiously, there was only a trace of a mustache. The breasts were large, pendulous and flabby and were particularly conspicuous because of exceptionally large, florid and pigmented areolae. The clitoris was about three times the normal size. In millimeters of mercury, the blood pressure was 160 systolic and 110 diastolic. The ocular fundi and the retinal vessels appeared to be normal.

Fig. 2.—Appearance of patient's face; *a*, before operation; *b*, five months after operation.

As the examination proceeded, the possibility of an adrenal cortical tumor naturally suggested itself, so that one was mentally prepared, on examining the abdomen, to find a mass in either renal region; however, the upper part of the abdomen was disappointingly normal and when, on bimanual pelvic examination, the mass, which by all the rules of the game should have been situated beneath the costal margins, was encountered deep in the pelvis, the resulting surprise was decidedly disconcerting. Nevertheless, as one reviewed the history of the girl's illness and re-examined her physically, the conviction grew that she almost certainly had to have a tumor comprised of hyperfunctioning adrenal cortical tissue. If this were the case the pelvic tumor would have to be an incidental abnormality, such as an ovarian cyst unrelated to the clinical picture or an aberrant adrenal cortical tumor. With these thoughts in mind we conducted the following laboratory studies:

Routine urinalyses, flocculation tests for syphilis, roentgenograms of the skull and thorax gave results that were either negative or normal. A soft tissue mass containing zones of calcium was noted in the roentgenograms of the pelvis. None of the roentgenograms showed any evidence of osteoporosis. The value for the hemoglobin was 17.0 Gm. per 100 c.c. of blood. The leucocytes numbered 9,900 per cubic millimeter. Unfortunately, an erythrocyte count was not made nor were the blood smears studied hematologically. Chemical studies of the blood gave the

following values, all of which are expressed in milligrams per 100c.c.: blood sugar, 68; plasma chlorides (as NaCl), 594; serum sodium, 342, serum potassium, 20.2. The carbon-dioxide combining power of the plasma was 52.2 volumes per cent. The urinary excretion of 17-ketosteroids per twenty-four hours, as determined by the Callow colorimetric method, was 54.6 mg. (The normal value for women is about 10.0 mg. in twenty-four hours; the range is 6 to 17 mg.) Urinary assays for estrin (estrogenic substance) and normal amounts of prolan (gonadotropic substance)* gave the following values in rat units per twenty-four hours: estrin 19; prolan less than 10.

Fig. 3.—Appearance of patient's body five months after operation.

The results of these studies strengthened our tentative diagnostic opinion. Consequently one of us (E. J. K.) felt that a probable diagnosis of "adrenal cortical tumor of the ovary" was warranted.† Accordingly, it was decided to explore the pelvis surgically, first treating the patient

*Frank technique.

†Not being handicapped by too much knowledge of unusual ovarian tumors and being skeptical that "luteomas" ever caused masculinity. I did not have too many misgivings when I offered this somewhat unusual diagnostic suggestion.—E. J. K.

preoperatively as though she had an adrenal cortical tumor and then, if the biopsy of the tumor revealed an adrenal type of cell, to continue with the postoperative treatment which has been used at the clinic in cases of this type of tumor. (Previous experience with tumors of the adrenal cortex has more than justified the wisdom of this procedure.)[13, 26]

Accordingly, on August 19, 1942, an exploration of the pelxis through a low midline incision was made by one of us (J. T. P.). A lobulated encapsulated tumor about the size of a cantaloupe was found. The tumor was yellowish in color, firm in consisteney and free from any attachments except the right Fallopian tube which lay stretched out over the capsule. The tumor, which appeared to take the place of the right ovary, was accordingly removed, along with the right Fallopian tube and the appendix.

Examination of fresh sections of the tumor prepared by the rapid freezing technique and stained with polychrome methylene blue resulted in a diagnosis of "probable adrenal cortical tumor of ovarian origin," and the patient was accordingly treated postoperatively as had been planned.*

The patient had an uneventful convalescence. At the time of her dismissal her appearance had started to change for the better.

On January 4, 1943, the patient returned for re-examination as requested. During the intervening five months many of the manifestations of her illness had disappeared. One month after her operation she had a normal menstrual period and her periods remained regular and normal thereafter. A remarkable change in her appearance has occurred (Figs. 2, 3*A* and *B*). The abnormal cutaneous hair was almost entirely gone. There remained a masculine pubic hair line, the faintest suggestion of a mustache and three or four short black hairs between the breasts. She stated that after her operation the hair of the scalp came out and was being replaced by a finer, more feminine type of hair. Her mannerisms were now distinctly feminine. She had no complaints except that she became tired much more easily than she had previously. She also remarked that her grades in school were not as good as they had been and that she had lost interest in her school work in general. Her mother called attention to the fact that whereas previously the patient had never been afraid of anything, now she became frightened rather easily and objected to being left alone in the house. Her weight was now 132 pounds (59.9 kg); the blood pressure varied from 138 mm. to 140 mm. systolic and from 80 mm. to 100 mm. diastolic. The value for urinary 17-ketosteroids was 2.6 mg. per twenty-four hours.

Grossly, the tumor measured 15 by 14 by 9 cm. and weighed 650 Gm. It was orange-yellow in color, coarsely lobulated in outline, and entirely invested by a smooth, glistening, grayish capsule which was free from adhesions. A pedicle measuring 6 cm. along its edge of attachment and 1 cm. in width consisted of the mesosalpinx which, like the right Fallopian tube, lay stretched out over the surface of the tumor. Surfaces made by cutting (Fig. 4) revealed that the substance of the tumor was bright yellow in color except for several small zones where hemorrhage

*The preoperative and postoperative treatment was as follows: Immediately before and after the operation the patient was given 1 liter of physiologic salt solution intravenously. Two liters were given daily thereafter for two days and one liter daily for two additional days. Five milligrams of desoxycor icosterone acetate was given daily for four days, beginning with the day of the operation. Twenty cubic centimeters of adrenal cortical extract was given when the patient returned from the operating room; 5 c.c. every three hours thereafter until eleven doses had been given, whereupon the dose was reduced to 5 c.c. every six hours for the next thirty-six hours. By this time the patient was well on the road to recovery and hormonal therapy was discontinued but physiologic salt solution was administered by mouth for the next two days.

imparted a dark, reddish appearance. Consistency was solid throughout. A pronounced degree of lobulation was present, the more superficial nodules of which corresponded to the external bosselations described previously. In the center of the mass was a calcified nodule, 2 cm. in diameter, apparently representing the zone of radio-opacity noted by the roentgenologists.

In preparations stained with hematoxylin and eosin the outstanding microscopic characteristic of the tumor was an essential composition of large pale polygonal cells arranged in anastomosing cords, sheets and irregular strands but rarely in structures approaching an acinar arrangement. Cellular groups were aggregated to form lobules of variable size and between these lobules bundles of fibrous tissue formed a coarse type of scaffolding. From these fibrous tissue septa small groups of fibroblasts spread in a radiating manner to surround the smaller units of tumor cells. Focal nests of lymphocytes were seen in the stroma (Fig. 5a). With higher magnification, the tumor cells were seen to be

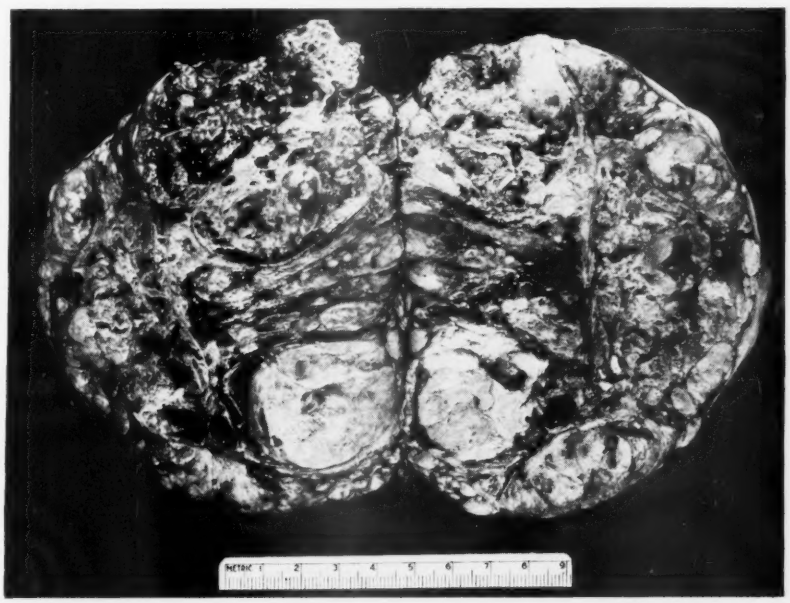

Fig. 4.—Cut surface of tumor; the dark areas represent hemorrhage within the tumor substance; remaining portion was of a bright orange-yellow color.

epithelial-like, large and polygonal, with fairly sharp outlines. Cytoplasm was voluminous and filled with rounded vacuoles which varied in size and number directly with the size of the individual tumor cells (Fig. 5b). Nuclei were large, centrally placed, and each possessed a sharp nuclear membrane. Nucleoli were prominent and usually single, but multiple nucleoli sometimes were observed. Multinucleated cells were occasionally noted in normal and in giant cell forms and this picture recalled a similar common observation in adrenal cortical tumors (Fig. 6). Mitosis was fairly frequent. Because of the cellularity, mitotic activity, size of nucleoli and variation in staining qualities of cells, the neoplasm was adjudged malignant grade 2 on the basis of 1 to 4 (by the method of Broders). Blood vessels were numerous and the larger ones were well formed. The smaller ones coursing between the smaller columns of tumor cells were often represented by blood filled spaces lined by a single layer of endothelium.

Special stains for lipoid demonstrated large amounts of this substance in the cytoplasm of the polyhedral cells (Fig. 7*A*). It varied in amount and one gathered from a study of the slides that many of the tumor cells were enlarged chiefly because of their high content of lipoid. Many of the smaller tumor cells appeared to be arranged in groups or islands and in these the fatty droplets were small in size and few in number.

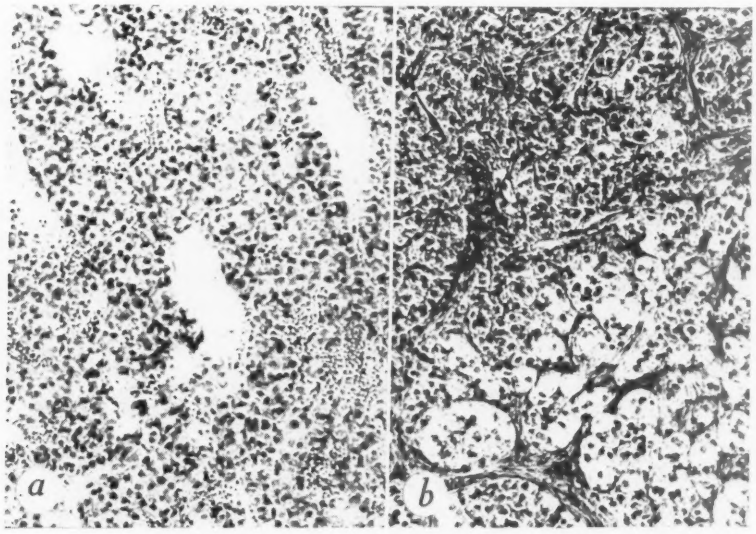

Fig. 5.—*a*, Anastomosing cords of tumor cells recall the structure of the suprarenal cortical tumors; blood vascular spaces are abundant and there are occasional accumulations of lymphocytes; stained with hematoxylin and eosin (×100); *b*, large, polygonal, pale and vacuolated tumor cells; some variation in size can be noted (the largest cells contain the most lipoid); definite organization into cords and strands is apparent and the individual units are separated by fine bands of connective tissue; stained with hematoxylin and eosin (×100).

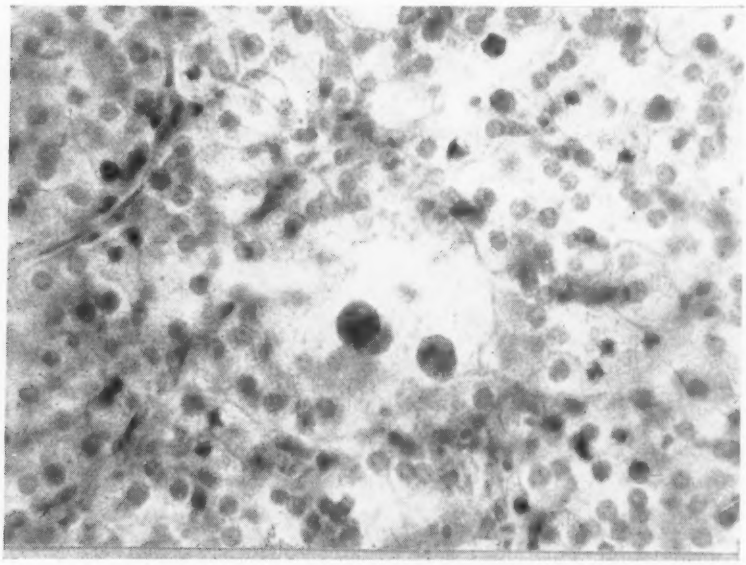

Fig. 6.—Much nucleated giant cells in this tumor appear to relate it to tumors of adrenal-cortical origin; stained with hematoxylin and eosin (×280).

Blocks of tissue preserved in absolute alcohol were stained for glycogen. This substance was demonstrated in different portions of the tumor (Fig. 7*B*) but in a rather spotty distribution. Its presence in the cytoplasm in general was in inverse proportion to the amount of lipoid. Sections made from blocks of tissue that had been fixed in Zenker's solution were stained with Ponceau-fuchsin stain.[9] Many of the cells contained the specific granules that are regarded by Broster and Vines as indicative of "androgenic" tissue (Fig. 8*A*). Slides made from de-

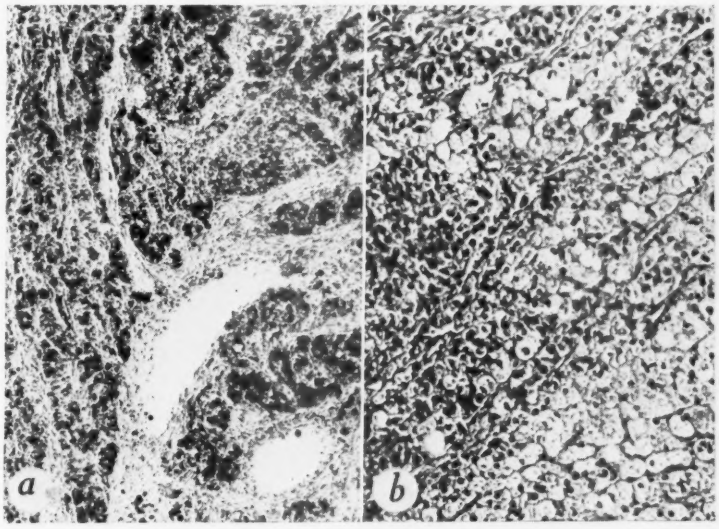

Fig. 7.—*a*, The high lipoid content of the tumor cells is well shown; stained with sudan III (×50); *b*, a positive test for glycogen is indicated by the small, darkly stained tumor cells; stained with carmine (×95).

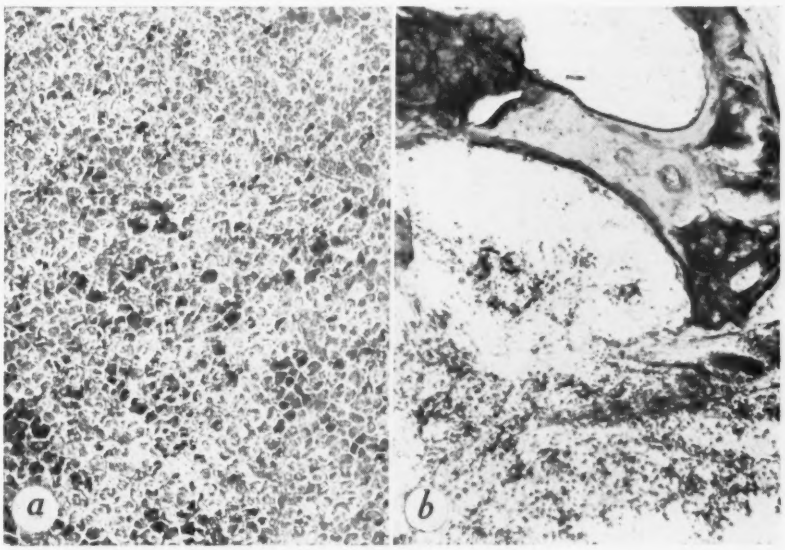

Fig. 8.—*a*, Darkened cells indicate a positive fuchsinophilic reaction; stained with Ponceau's fuchsin stain (×95); *b*, ossified nodule from center of tumor showing well-formed bony trabeculae and marrow elements; stained with hematoxylin and eosin (×85).

calcified portions of the calcified nodule noted in the roentgenogram revealed irregular calcification and also focal ossification. The osseous tissue appeared to be true bone with well formed haversian canals and islands of fairly normal looking bone marrow (Fig. 8*B*). The capsule of the tumor appeared everywhere intact superficially but more deeply it revealed small islands of invasion by neoplastic tissue. In most of the sections studied, tissue resembling ovarian stroma could be identified and in one the presence of a corpus fibrosum and a primordial follicle established beyond question of doubt that the neoplasm was of ovarian origin (Fig. 9). Except for the presence of bone and ovarian tissue, the preceding description could be applied to the general run of adrenal cortical tumors.

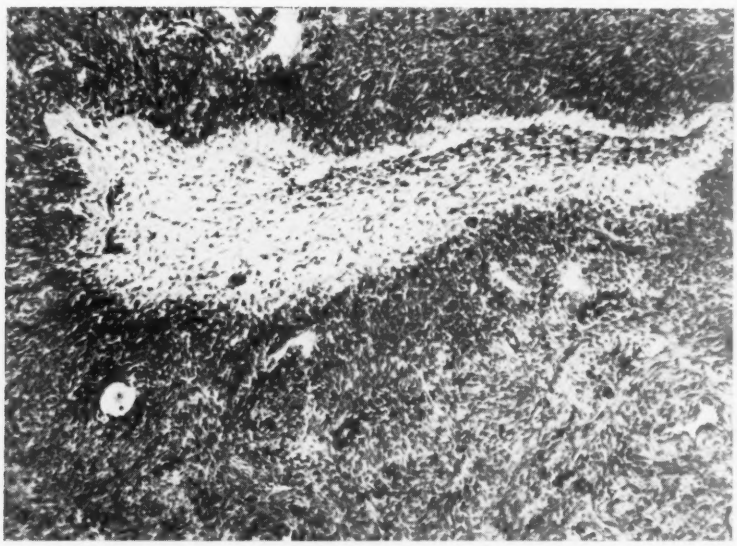

Fig. 9.—Portion of capsule of tumor; the corpus fibrosum and primordial follicle identify the tissue as being truly ovarian, stained with hematoxylin and eosin (×80).

Comment on Cases

Tables I and II summarize the clinical and pathologic data in the case which we have just reported (case 14) and in thirteen additional cases previously reported in the literature. Certain features are deserving of special emphasis. Hirsutism was present in all fourteen cases and varied in duration from nine months to thirteen years. A masculine pattern of distribution of hair usually was noted. This was emphasized in four instances by an observed recession of the hair line along the forehead, with the notation that the patients were partially bald.

In ten of the fourteen cases the habitus was described as being of masculine type with pronounced development of the muscles of the shoulder girdle. In eight of the fourteen cases there was a definite and sometimes pronounced gain in body weight. Moreover, in the majority of the observed instances the obesity was more or less localized to the face, cervical region and pectoral girdle.

Blood pressure readings were recorded in six of the twelve cases that were reported more recently. In four of these cases, hypertension was present with systolic pressures in excess of 140 mm. or diastolic pressures of more than 90 mm. of mercury. In the case we have just reported, postoperative readings of the arterial blood pressure indicated a moderate drop in both systolic and diastolic pressures from distinctly high preoperative levels. This finding indicates that in some way the ovarian tumor was responsible for the observed arterial hypertension.

Diabetes or a diabetic tendency was of relatively frequent occurrence. In one of the fourteen cases, clinically recognized diabetes had been present for six years. Another patient had a trace of sugar in the urine but was apparently not otherwise investigated for evidence of diabetes. In another case the concentration of blood sugar was 150 mg. per 100 c.c. and in two additional cases the presence of subclinical diabetes was indicated by abnormal glucose tolerance curves.

Hematologic observations suggesting polycythemia vera were unusually common in the group. Blood counts were recorded in eight of the fourteen cases and in four of these the number of erythrocytes exceeded 5,000,000 per cubic millimeter of blood. In one of these cases the erythrocytes numbered almost 9,000,000 per cubic millimeter and dropped to 6,000,000 after removal of the tumor.

In a number of instances, the blood and urine were studied for various hormonal substances. In the case reported by Saphir and Parker (case 5) the urine contained 5,000 mouse units of estrogenic substance per liter and 66 mouse units of gonadotropic substance per liter. In another case, reported by Novak and Wallis (case 6), estrogenic substance could not be detected in the urine before operation but 200 mouse units per liter were found afterwards. In the case reported by Maxwell (case 7), 40 mouse units of estrogen were present in 1 liter of urine but gonadotropic substance was absent. Quantitative estimation of androgenic material by the Capon method was made in one of the two cases reported by Rottino and McGrath. Values obtained were 17.3 and 15.7 international units. In the same case, the value for estrogens was 3.3 rat units per liter.

From the pathologic standpoint, all of the tumors have been unilateral with but one exception, in which both the right and left ovary equally shared the dubious honor of being host. Size has varied from nodules of microscopic dimensions to masses measuring 16 by 14 by 9 cm. The tumors were for the most part yellowish in color and encapsulation was the rule in practically all recorded instances. Microscopically, the tumors were composed of large, pale, polyhedral, epithelial-like cells disposed in cords and anastomosing strands. Large amounts of intracellular lipoid material were noted in nearly all cases and intercellular glycogen was occasionally found to be present. Ponceau-fuchsin stains were employed in most of the cases recently reported and these tests yielded positive results in three cases. In twelve of the fourteen cases,

TABLE I. COMPARATIVE CLINICAL DATA

CASE	AUTHOR	AGE (YR.)	PARITY	HIRSUTISM	MASCULINE HABITUS	VOCAL CHANGES	HYPERTROPHY OF CLITORIS	OBESITY OR GAIN IN WEIGHT	AMENORRHEA	HYPERTENSION	DIABETES	OUTCOME
1	Bovin, 1908	28	Multiparous	+ (6 years)	Not stated	Not stated	Not stated	Not stated	+ (7 years)	Not stated	Not stated	Recovery. Patient later became pregnant.
2	Bingel, 1924	47	Para iv	+ (13 years) Partially bald	+ (10 years)	+ (10 years)	Not stated	+	+ (13 years)	Not stated (severe headaches)	(6 years)	Feminine habitus in 3 years. (Partial relapse.)
3	Sellheim, 1925	49	Para ii	+ (6 years) Partially bald	+ (6 years)	+ (6 years)	+	+	+ (6 years)	Not stated	Not stated	Feminine habitus in 1 year.
4	Cosacesco et al., 1931	34	Para 0	+ (5 years) Partially bald	+ (5 years)	+ (5 years)	+	0	+ (7 years)	Not stated	Not stated	Completely feminine in 2½ years.
5	Saphir and Parker, 1936	15	Para 0	+ (1 year)	0	+ (1 year)	0	+ (1 year)	+ (1 year)	Blood pressure 110 to 130 mm. systolic and 70 mm. diastolic	0	Partial return to normal in 1 year.
6	Novak and Wallis, 1937	32	Para 0	+ (2 years)	+ (Months)	+ (2 years)	+	Slight	+ (2 years)	Systolic blood pressure 145 mm.	Fasting blood sugar 150 mg. per 100 c.c.	Normal feminine habitus in 1 year.
7	Maxwell, 1937	62	Para 0	+ (5 years) Partially bald	+ (10 years)	+	+	Not stated	0 (postmenopausal)	Blood pressure 200/100	Diabetic type of glucose tolerance curve	Improvement in 4 months.

TABLE I—CONT'D

8	Novak, 1938	37	Not stated	+	+	+ Voice deep but feminine	+	+	+ (3 years)	Blood pressure 130/90	0	Normal habitus in 3 years.
9	Novak, 1938	27	Not stated	+ (9 mo.)	+	+ (9 mo.)	+	Not stated	+ (1 year)	Not stated	0	Menses became normal within 3 months.
10	Rottino and McGrath, 1939	23	Para i	+	+ (4 years)	+	+	+ (5 years)	+ (3 years)	0	Diabetic type of glucose tolerance curve	Seminormal habitus in 18 months. Blood sugar curve still abnormal at 6 months.
11	Rottino and McGrath, 1939	30	Para 0	+ (5 years)	0	+ (5 years)	0	+ (caused by ascites?)	0 (after hysterectomy)	Blood pressure 130/70	0	Temporary improvement; recurrence; death in 4 years.
12	Bauer, 1939	32	Para i	+	Not stated	0	+	+	+ (3 years)	Not stated	? (trace of sugar in urine)	Died at operation.
13	Blackmun, 1942	23	Para 0	+ (3 years)	+ (3 years)	+ Voice husky	+	+ (30 lb. gain)	+ (1 year)	Not stated	Diabetic type of glucose tolerance curve	Improvement in 1 year.
14	Dockerty and Kepler, 1943*	16	Para 0	+ (2 years)	+ (1 year)	0	+	+ (20 lb. gain)	+ (2 years)	+ Blood pressure 160/110	0	—

*This case has been reported in the present paper.

TABLE II. COMPARATIVE PATHOLOGIC DATA

CASE	AUTHOR	SIDE INVOLVED	SIZE, CM.	COLOR	PRESENCE OF CAPSULE	TRABECULATION	PRESENCE OF LIPOID	FUCHSINOPHILUS GRANULES	PRESENCE OF GLYCOGEN	IDENTIFICATION OF OVARIAN ORIGIN	SIGNIFICANT LABORATORY DATA
1	Bovin, 1908	Left	8 by 8 by 6	Yellow	+	+	+	Test not then available	Not stated	+	0
2	Bingel, 1924	Right	9 by 4 by 4	Yellow	+	+	+	Test not then available	Not stated	Not stated	Erythrocyte count, 8,900,000
3	Sellheim, 1925	Left	"Chestnut"	Grayish-red	+	+	0	Test not then available	0	Not stated	0
4	Cosacesco et al., 1931	Left	Nodule in wall of cyst 5 cm. in diameter	Yellow	+	+	+	Test not then available	Not stated	+	0
5	Saphir and Parker, 1936	Right	Microscopic	Not stated	+ Consisted of normal ovarian tissue	+	+	Not stated	Not stated	+	Increase in urinary estrogens
6	Novak and Wallis, 1937	Right	13 by 8 by 5	Orange-yellow	+	+	+	Not stated	Not stated	+	Erythrocyte count, 6,600,000

TABLE II—CONT'D

7	Maxwell, 1937	Left	Microscopic	Not stated	+	Not stated	+	Not stated	Not stated	+	Increase in urinary estrogens; erythrocyte count, 6,100,000
8	Novak, 1938	Right	6 (diam.)	Orange	+	+	+	Not stated	Not stated	+	0
9	Novak, 1938	Right	2 (diam.)	Yellow	+	+	+	Not stated	Not stated	+	0
10	Rottino and McGrath, 1939	Right	4 by 1.5 by 1.5	Orange	+	+	+	0	0	+	Urine positive for estrogens and gonadotropins
11	Rottino and McGrath, 1939	Bilateral	3 (diam.) 4 (diam.)	Orange	Not stated	+	+	Not stated	Not stated	+	0
12	Bauer, 1939	Left	14 by 13 by 5	Not stated	Not stated	+	+	+	Not stated	+	0
13	Blackmun, 1942	Left	4 (diam.)	Yellowish gray	+ (cystic)	+	+	+	Not stated	+	0
14	Dockerty and Kepler, 1943*	Right	15 by 14 by 9	Yellow	+	+	+	+	+	+	Value for hemoglobin 17 Gm. per 100 c.c. of blood

*This case has been reported in the present paper.

the presence of ovarian tissue was demonstrated microscopically in the tumor capsule. In another case there was gross evidence for an ovarian point of origin. In the case reported by Bovin (case 1), ovarian involvement was very definite, but an origin from the homolateral broad ligament could not be entirely excluded.

As is true with most neoplastic newcomers, there was much hesitation in deciding the question of malignancy. The case reported by Rottino and McGrath (case 10) provided an answer or the confirmation when the patient died of metastasis. In this case the tumors (bilateral) differed in no essential microscopic detail from many of the others which had been regarded by the authors as being benign. In the case that we have reported in this paper (case 14 in the tables) the malignancy of the tumor was grade 2 according to the method of Broders.

The tumors under consideration may be studied from three distinct angles, namely: (1) structure and histogenesis; (2) clinical manifestations, and (3) pathologic physiology as shown by the presence of hormonal substances in the urine. Each of these three approaches has its distinct limitations. Consequently, any theory regarding the nature of these tumors must take into consideration the factual data derived from all three types of approach.

Histogenesis.—Histologically, these tumors conceivably might arise from one of the following structures: (1) the adult corpus luteum; (2) a pre-existing granulosa-cell tumor; (3) an adrenal cortical ovarian rest, and (4) through excessive development of certain cellular elements (adrenal cortical?) in a teratomatous growth. In 1921, Ernest Glynn analyzed critically most of the literature on yellow tumors of the ovary including a number of lesions that had been labelled "hypernephromas" and ascribed in point of origin to adrenal cortical rests in the ovary. Glynn's investigation led him to the belief that these tumors had no connection with adrenal tissue whatsoever, but were, for the most part, derived from the corpus luteum. He based his arguments on clinical as well as histologic grounds, and pointed out that the tumors never cause masculinization as did adrenal cortical tumors. The case reported by Bingel (case 2) apparently escaped his notice and the masculinizing tumor in the case reported by Bovin (case 1) he relegated to an origin in the broad ligament, with secondary invasion of the ovary. (He apparently was ready in this latter case to concede an origin from heterotopic adrenal tissue.) The cases reported by Bovin and by Bingel (cases 1 and 2) were the only two which antedated the publication of Glynn's splendid article. In the light of recent investigations, it now appears that several of Glynn's "hypernephromas" conceivably may have been of corpus luteum origin. Two appear to be undoubted examples of compound lutein cysts associated with hydatid mole. Pathologically, however, most of the remainder clearly represent examples of luteinized granulosa-cell tumors with clinical symptoms of feminization

and not masculinization. Were Glynn now to analyze the examples of yellow masculinizing ovarian tumors which have been described since 1921, there is no doubt that some of his arguments for a corpus luteum origin would lose much of their force. Schiller logically pointed out that the corpus luteum is ordinarily a transient structure derived from two pre-existing cellular elements in the ovary, namely, granulosa cells and theca cells. From the granulosa cells are derived the well-known granulosa-cell tumors which may in some cases become luteinized, in which case they have been called "luteomas." From the theca cells arise the theca cell tumors. Both of these tumors are "feminizing." Neither is associated with virilism or the other symptoms which accompany the tumors under consideration. Furthermore, according to Schiller, it seems highly unlikely that any type of tumor composed of corpus luteum cells could possibly produce virilism, striae, hypertension, osteoporosis, diabetes (that is, Cushing's syndrome) when one considers what is known concerning the hormonal function of the corpus luteum. Certainly these symptoms are entirely out of line with what one would expect from hyperfunctioning cells of the corpus luteum.*

Both the gross appearance and the histologic structure of the present group of tumors suggest an adrenal cortical origin. If this were the case one would expect that the incidence of these tumors could be correlated with the incidence of adrenal rests within the substance of the ovary. However, according to the best figures available, it is impossible to make such a correlation. In fact, it appears that adrenal rests within the ovary occur even less frequently than do these adrenal-like tumors.† Adrenal cortical rests occur elsewhere in the body with considerable frequency,[16] and there are a few clear-cut examples of ectopic adrenal cortical tumors that have arisen from such rests.[14] However, as yet there is no conclusive evidence that ectopic adrenal tissue within the ovary has given rise to an ectopic adrenal tumor, unless the tumors under consideration ultimately will be proved to be examples of such an occurrence.

The presence of glycogen, noted in several of these tumors, has led to the belief that the tumors were of adrenal origin. However, we now know that the corpus luteum, on the one hand, and adrenal adenocarcinoma, on the other, also contain small or large amounts of this substance. It is doubtful, therefore, if the presence of glycogen in any given tumor can be taken as evidence of its histogenesis. This argument applies with equal force to a positive reaction with the Ponceau-fuchsin stain. This stain, originally considered specific for cells of the andro-

*On the other hand, many of the symptoms of adrenal cortical tumor are not those that one would expect from what is known regarding the physiology of the adrenal cortex.

†Grollman, however, expressed the opinion that adrenal rests within the ovary occur fairly commonly during infancy, but that they are composed of androgenic tissue and regress during childhood along with the androgenic tissue of the adrenal cortex. Incidentally, according to the same author, it is this androgenic tissue, which fails to regress and ultimately becomes hyperplastic or neoplastic, that gives rise to the sexual abnormalities seen in conjunction with adrenal cortical tumors or with adrenal virilism associated with bilateral adrenal cortical hyperplasia. This intriguing conception conveniently ignores many of the metabolic symptoms, such as diabetes, hypertension and osteoporosis and others that commonly occur in conjunction with either adrenal cortical neoplasms or hyperplastic lesions.

genic adrenal type has been found to react positively with the cells of the corpus luteum. Sharp cytoplasmic outlines of tumor cells have been interpreted as indicating an adrenal origin for these ovarian tumors but the degree of sharpness has been found to depend more upon the size and the number of lipoid droplets than upon any fundamental difference between an adrenal cortical and a corpus luteum cell.

It may thus be seen that from the standpoint of pure cytology the origin of these tumors is a histogenic jigsaw puzzle. In the case that we have reported, the finding of well-formed, marrow-bearing bone early raised our hopes that we had the answer to this puzzle in a clear teratomatous origin. Careful search, however, failed to reveal the presence of any other unusual tissue types and we were left to face the bleak fact that calcification and even ossification may occur in any type of neoplasm. Consequently, the theory of a teratomatous origin must remain as an unproved possibility.

Clinical Manifestations.—The endocrine symptoms of adrenal cortical tumors vary qualitatively and quantitatively in individual cases. A comparable variability appears, possibly to a lesser extent, to run through the group of ovarian tumors under consideration. Nevertheless, in spite of this variability, the composite clinical picture of the one group has much in common with the composite clinical picture of the other. For example, each group of tumors tends to be characterized by pathognomonic changes in the facies and habitus which were so graphically described by Cushing. In addition, one can mention amenorrhea, hirsutism, acne, enlargement of the clitoris and other symptoms usually considered to be indicative of masculinization. Of particular interest, however, is the occurrence in each group of an unusual combination of symptoms, namely, hypertension, polycythemia and diabetes. Polycythemia, for example, although not a particularly common symptom of adrenal cortical tumor, may be present to such an extent that all the common hematologic criteria necessary for the diagnosis of polycythemia vera can be obtained. The occurrence of severe polycythemia (approximately 9,000,000 erythrocytes per cubic millimeter) in case 2 in Table II is, therefore, particularly suggestive that in this instance the tumor was in fact a tumor of the adrenal cortex. Diabetes, likewise, does not occur regularly in cases of adrenal cortical tumor. Nevertheless, in a case recently reported by Sprague, Priestley and Dockerty it was the only endocrine manifestation of an adrenal cortical tumor. The relatively high incidence of diabetes in the fourteen cases listed in Table I has already been noted.* The foregoing remarks relative to polycythemia and diabetes are equally applicable to hyperten-

*The occurrence of diabetes in this type of case suggests an overproduction of the adrenal "diabetogenic hormone" (11 dehydro-17 hydroxy corticosterone or compound E of Kendall and compound Fa of Reichstein) by the tumor, whereas the presence of hypertension might be taken as indicative of an excessive production of some compound similar to desoxycorticosterone. As yet there is no adequate explanation for the occurrence of polycythemia. For a stimulating discussion of the pathologic physiology of Cushing's syndrome and allied disorders the reader is referred to Fuller Albright's article in the 1943 *Harvey Lectures.*

sion. All three of these symptoms, which dovetail nicely with what is known regarding the normal and abnormal physiology of the adrenal cortex, strongly suggest that, if these ovarian tumors are not in reality ectopic adrenal cortical tumors, they function as such and have common pathophysiologic denominators with them.

At this point it is well to re-emphasize that none of the metabolic symptoms which have been mentioned occur regularly in conjunction with arrhenoblastoma.[17] This tumor masculinizes its host but does not cause hypertension, diabetes, polycythemia, purplish striations or plethoric obesity. In fact, the symptoms which do occur are precisely those which one would expect and following the prolonged administration of large doses of testosterone proprionate to women or eunuchoid men.

Urinary Hormonal Substances.—At first thought it might be inferred that the probable origin of adrenal-like ovarian tumors might be determined by chemical analyses or bio-assay of the urine for hormonal or hormonal-like substances. Here also one encounters difficulties, because in cases of proved adrenal cortical tumors a variety of these substances have been found in the urine by various workers at various times. Among these are estrogenic substances, androgenic substances, substances which are said to prolong the lives of adrenalectomized animals, 17-ketosteroids and inactive compounds which are related chemically to the hormonal ketosteroids.

If one accepts the validity of these conflicting observations, the only permissible conclusion is that histologically similar adrenal cortical tumors have differing functional capacities. The variation in the clinical pictures lends weight to this view. At present, the tendency is to emphasize the significance of the presence of excessive quantities of 17-ketosteroid material in the urine. From our own experience with a number of unreported cases of proved adrenal cortical tumor, we have reason to believe that the excessive excretion of these compounds is not necessarily a concomitant of adrenal cortical tumor, and, furthermore, that when these compounds are excreted, the values obtained do not by any means parallel the intensity of the clinical picture. When we turn to the ovarian counterparts we again find the same type of variability but less easily demonstrated because of the limited number of observations. To exemplify, in the case reported by Saphir and Parker (case 5), an unusually high titer of urinary estrogens was obtained. In contrast, in most of the other cases in which this determination was made, the values were normal or subnormal. In the case that we have reported, the excretion of estrogens was within normal limits, but the excretion of 17-ketosteroids was definitely excessive.* This observation

*A large amount of urine was obtained for study of the particular ketosteroids that were responsible for the high qualitative values that were obtained. Unfortunately, through a technical error in extracting the urine the results were completely vitiated except for the extraction of a few milligrams of androsterone which is without significance. It is well to bear in mind that the colorimetric reaction on which the determination of the 17-ketosteroids is based is a group reaction which is not specific for any one substance.

further supports the view that the functional behavior of the tumor was compatible with that of a tumor of the adrenal cortex; however, it does not necessarily exclude other possibilities.

Summary

Like arrhenoblastomas, the adrenal-like ovarian tumors tend to masculinize their hosts but the tendency toward the production of a bizarre type of fat distribution, the occurrence of purplish striae, arterial hypertension, polycythemia and so forth, relate them more closely to adrenal cortical carcinomas from a functioning standpoint. Histologically, the tumors do not appear to arise through luteinization of pre-existing granulosa-cell neoplasms and an origin from adrenal cortical rests seems more logical than does a derivation from corpora lutea. An origin by way of teratomatous development likewise remains unproved. Some of the tumors appear to be cytologically malignant and in one instance death resulted from metastasis.

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ADRENAL REST TUMOR OF THE OVARY

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ADRENAL rest tumors of the ovary are a form of tumor frequently, but not invariably, associated with defeminization and masculinization of the female.

The scientific literature contains very few reports of such a type of tumor, and much confusion exists insofar as the histogenesis and pathology of the tumor are concerned.

In 1939, Van Kirk and Edwards[1] could collect only 27 such cases, some of which were not positively identified as primary in the ovary. Peham[2] is accredited with having reported the first case in 1899.

Rottino and McGrath,[3] later in 1939, reported that only seven cases recorded previously in the literature could be accepted as being of true adrenal rest origin; and they summarized these seven cases, adding two additional cases of their own finding. They accredited Bovin[4] with having reported, in 1908, the first adrenal rest tumor of the ovary.

Most authors agree that the adrenal rest tumor of the ovary arises from misplaced cell inclusions of the adrenal cortex or from mesenchymal cells in the ovary destined to produce adrenal cortex, rather than from lutein cells. That such rests do occur was shown by Marchand,[5] who, as early as 1883, demonstrated accessory nodules of suprarenal gland tissues in the broad ligaments.

Embryologically, the ovaries, testes, and adrenal cortex have a common origin, being derived from the coelomic epithelium of the urogenital fold. This urogenital fold in later embryonic life divides to form the adrenal cortex and the gonads. It is not without possibility, therefore, that misplacement of cells occasionally occurs in the ovary from the neighboring adrenal *anlage*. Schiller,[6] after careful histopathologic study, demonstrated adrenal rests in 20 per cent of infants' ovaries. Novak[7] states that aberrant adrenal rest tissue is not infrequently seen, especially along the course of ovarian or spermatic vessels. He adds that adrenal rests are rare in the ovary, but have been noted in the cortex, hilum, and near cysts. Other adrenal rests have been reported in the broad ligament, ovarian ligaments, uterus, inguinal canal, epididymis, and even in the liver near the adrenal gland.[8-10]

The mere presence of adrenal tissue in an aberrant site does not necessarily mean that the clinical signs of masculinization will always be present. The tendency for aberrant adrenal tissue to become neoplastic cannot be doubted, however.

Objections to adrenal rest tumors being primary in the ovary have been voiced by some investigators, who believe that such tumors develop from accessory adrenal cell inclusions which are present only in the broad ligament.

Glynn[9] denies even the existence of adrenal rest tumors and states that all such tumors thus classified are of lutein origin. Novak admits that luteomas do exist, but believes that the vast majority of these tumors are of an adrenal rather than of a lutein origin. Schiller accepted only 3 cases from the literature as being examples of ovarian luteomas.

Because of the confusion which exists in the histopathology of adrenal rest tumors, they have been reported in the literature under varying classifications and an adequate survey of the literature is thereby almost impossible. The tumor has been variously referred to as primary hypernephroma of the ovary, hypernephroid tumor of the ovary, interrenaloma of the ovary, cortical adrenal tumor of the ovary, adrenal rest tumor of the ovary, and luteoma. In 1939, Rottino and McGrath suggested the term "masculinovoblastoma" as a name being descriptive of its biologic properties and to differentiate the tumor from arrhenoblastoma.

From the recorded cases, no correlation appears to exist between the age of the patient and the occurrence of the tumor. The tumor has been observed at various ages from 3 to 65.

Stadiem[11] suggested that inasmuch as no case had ever been reported in a colored patient, this might be taken as a diagnostic hint. The majority of case reports, however, have come from European clinics where the Negro population is small. Our case refutes this hypothesis.

The tumor is generally unilateral, varying in size from several millimeters to 3 or 4 centimeters, occasionally slightly larger. It is most often noted in the hilar region of the ovary, although it may involve the whole ovary by contiguity. It is a solid tumor, often encapsulated, rarely becoming cystic, occasionally showing small areas of hemorrhage and necrosis on cut surface. The external surface is usually smooth. The tumor is generally of soft consistency, and has a characteristic yellow color, resembling closely its analogue, the adrenal.

Microscopically, the tumor is composed of numerous, conspicuously arranged, cords of cells or acini, separated by fibrous trabeculae, and composed of large, acidophilic cells having an abundant granular or spongy cytoplasm and a relatively large, round or slightly indented, dark staining, centrally placed nucleus. The cells are round, or more commonly, roundly polygonal. The cell outline is well defined, and the surface where the adjacent cells meet is usually flattened. The nuclear nucleoli are very prominent. Delicate capillaries and equally delicate connective tissue strands can be noted coursing through the acini. The

arrangement of cells often suggests that of the zona fasciculata or even the zona glomerulosa of the adrenal cortex.

Greenhill, Greenblatt, and Brown[12] reported in 1939 that adrenal cortical adenomas and adrenal rest tumors of the ovary presented not only comparative morphologic features and staining reactions, but also identical polariscope characteristics. This may serve as a basis for differential diagnosis from the luteoma with which the adrenal rest tumor of the ovary may be confused.

Hormone assay tests may also be of value in the differential diagnosis.[13] With adrenal rest tumors, a high level of estrin can be detected in the urine; whereas with the luteomas, corpus luteum hormone is found.[14]

Downes and Knox[15] demonstrated microchemically that the cells of adrenal rest tumors of the ovary contain lipids and glycogen. Ewing[16] states that glycogen occurs in the cells of embryonic tumors, and is especially abundant in the cells of hypernephroma, chorioma, and teratoma. Chemical analysis shows also the presence of phospholipids and cholesterol.

The androgenic substance or substances secreted by the adrenal rest cells produce a syndrome in the female of defeminization and masculinization, identical with that syndrome produced by the arrhenoblastoma. There is an amenorrhea coming on rather suddenly after previously regular menstrual periods, associated with a regression in the size of the breasts among older patients or arrested development in younger patients. Hirsutism appears, with the development of a chin and upper lip beard, a masculine pubic escutcheon, and the growth of coarse hair on the chest and extremities. Baldness results from a falling out of the hair over the head, while acne of the face and upper part of the trunk may sometimes be a prominent sign. There is a redistribution of the subcutaneous tissue, such that the body takes on a masculine appearance. Broadening of the shoulders and an increase in the firmness of the skeletal musculature are noted. The voice becomes deepened and more resonant as a result of hypertrophic laryngitis. Hypertrophy of the clitoris may be excessive, and there is frequently a loss of libido. Infertility, or sterility, may also be encountered.

It is probable that most of these tumors are benign, as is true of comparable lesions of the adrenal. Excision of the tumor frequently produces moderate to complete regression of all signs and symptoms. The voice changes, however, usually are permanent. If the hirsutism does not disappear postoperatively, the presence of additional adrenal cortical tissue in other aberrant locations is a possibility.

It is interesting to note that the sex hormone produced by the adrenal rest cells produces sex characteristics and changes not of the same but of the opposite sex.[17] In the male, the adrenal rest tumor is known to produce a female type of adiposity, breast hypertrophy, at times with lactation; testicular atrophy, and loss of libido. Schiller has

recorded two such instances of feminization associated with adrenal-like structures in the testicle. In children, the tumors bring about a precocious puberty.

The following case, which came under observation at Kings County Hospital in 1937, presents a clinical course and gross and microscopic findings typical of an adrenal rest tumor of the ovary.

Case Report

The patient, a 29-year-old Negro housewife, presented herself for admission to Kings County Hospital on October 21, 1937. Her chief complaint was that she had not menstruated for the previous four years.

The patient first menstruated at the age of 12, the menses recurring regularly thereafter at 28-day intervals, lasting 3 to 5 days. In 1933, the menses had suddenly ceased and had never recurred. Concurrently, the patient developed a dull ache in the left lower quadrant which radiated to the lumbar region of the back. The ache was persistent, and at times became quite severe. In 1934, the patient first noticed her voice becoming deeper in pitch. She first noticed a beard developing in 1935.

Past medical history was noncontributory. She denied venereal disease. She had had no previous operations or serious illnesses. She had never been pregnant.

Physical examination revealed a well-developed and well-nourished colored female. The voice was deep. The face was covered with a thick beard, which was especially marked on the upper lip. The hair of the body was masculine in character, the abdomen and back being covered by a considerable amount of small coarse hair. A masculine escutcheon was present. Lungs were clear to percussion and auscultation. Heart was not enlarged. Blood pressure was 120/70. The abdomen was obese, soft, not tender, and no abnormal masses were palpable.

Pelvic examination revealed a clitoris 4 or 5 times the normal size, the glans measuring 5 centimeters in length and 1½ centimeters in diameter at its base. The labia were not abnormal. The cervix was nulliparous, freely movable, and faced anteriorly. The uterus was firm, retrocessed, but freely movable. In the right fornix a nontender, somewhat nodular mass, the size of a small orange, was palpated. The left fornix and posterior cul-de-sac were clear.

The urinalysis was negative. Blood Wassermann was negative. Blood urea was 20 mg. per cent; creatinin 1.18 mg. per cent; sugar 88 mg. per cent. The white cells numbered 8,800 with 72 per cent polymorphonuclear leucocytes. The red cells numbered 4.3 million, and the hemoglobin was 80 per cent.

A roentgenogram of the abdomen showed no evidence of any mass displacing the intestinal tract. Retrograde pyelograms showed both kidneys to be normal in size and position, and no calculi were noted.

A preoperative diagnosis of arrhenoblastoma of the right ovary was established, and patient was prepared for operation.

On October 27, 1937, an exploratory laparotomy was performed through a suprapubic midline incision. The peritoneal cavity contained a small amount of clear fluid. The right ovary was the site of a hard tumor, the size of an orange, which was diffusely firm and showed no evidence of cystic degeneration. The tumor was attached by a wide

base which spread medially into the broad ligament. The tumor lay free, was not otherwise adherent to any viscera, and was freely movable. The right tube was intimately attached to the tumor along its entire length. Large varicosities were noted in the right broad ligament. The left tube and ovary appeared normal. The uterus was hypoplastic, but of the usual color and consistency, and freely movable. Both kidneys were palpated and felt to be of usual size. The adrenal glands were not palpable, and no abnormal masses were noted.

A right salpingo-oophorectomy was performed.

The postoperative course was uneventful. The patient was discharged to the outpatient department on the sixteenth post-operative day.

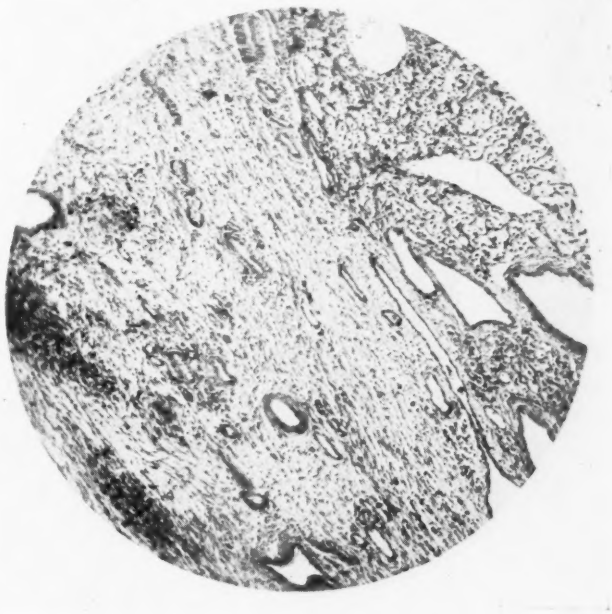

Fig. 1.—Low-power photomicrograph, showing the relationship of the adrenal tumor with the ovarian stroma.

Pathologic Report.—

The specimen consisted of a large, firm, somewhat nodular, tumor mass, measuring 7 by 5 by 3 centimeters. The capsule was grayish-white in color, was smooth externally, measured 1 to 2 millimeters in thickness on section. The tumor consisted of solid yellow tissue, arranged in alveolar formation, with intervening bands of gray fibrous tissue similar to that of the capsule. The alveolae were concentrically arranged about a small grayish center. The Fallopian tube appeared somewhat thickened, but showed no other gross changes.

Microscopically, all sections from various portions of the tumor revealed essentially the same architecture and consisted of diffuse palisaded sheets of moderate-sized round and polygonal cells having considerable amounts of acidophilic, spongy cytoplasm and small deeply-staining nuclei. The cells were arranged in acini and were supported by a delicate, vascular stroma, the cell borders being well-demarcated.

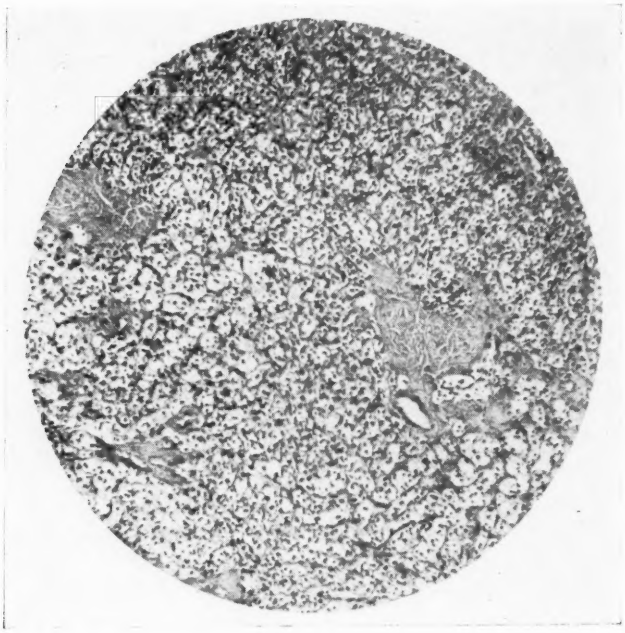

Fig. 2.—Low-power photomicrograph, showing the tumor divided by large fibrous septa into alveolar masses of diffusely palisaded cells closely resembling those of the adrenal cortex.

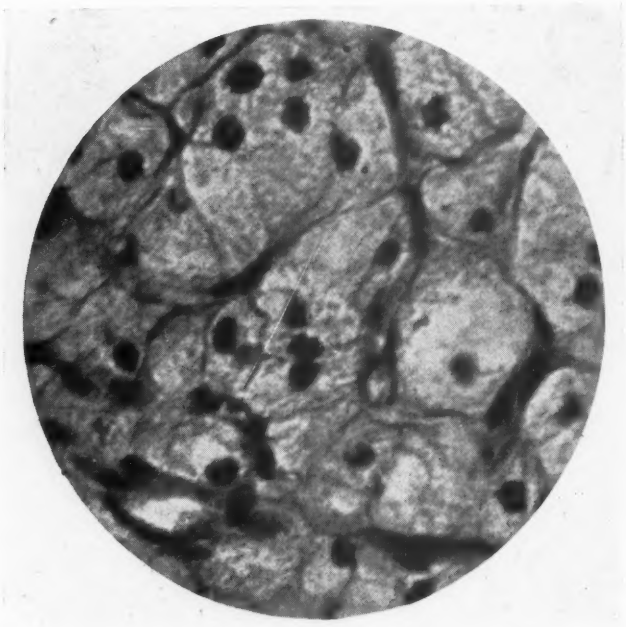

Fig. 3.—High-power photomicrograph, showing the large, well-defined, polygonal cells with abundant granular cytoplasm and round, deeply staining nuclei.

Large fibrous septa extended through the tumor and divided it into large alveolar masses. The cellular arrangement closely resembled that of normal adrenal cortex. Cross section of the Fallopian tube showed a chronic salpingitis.

The histopathological diagnosis was adrenal rest tumor of the ovary.

The patient subsequently returned to the outpatient department, six months postoperatively. At this time, she was again menstruating normally, the periods recurring regularly every 28 days and lasting 4 days. The hair on the face, abdomen, and chest was falling out and was noticeably diminished in amount and texture. Patient was last heard from on February 18, 1941, at which time she was applying for work as a domestic worker and was enjoying good health at that time. Recent efforts to locate the patient have been unsuccessful.

Summary

A case of adrenal rest tumor of the ovary, occurring in a colored female and associated with marked changes of defeminization and masculinization, is presented. Surgical removal of the tumor produced regression of most of the signs and symptoms. The patient, when last heard from, over three years after operation, was enjoying good health.

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INTRAVENOUS AMINO ACIDS IN NEPHROTIC TOXEMIA OF PREGNANCY*

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IT IS generally acknowledged that the pregnant woman requires about 15 per cent more calories, 25 to 50 per cent more iron, 20 to 25 per cent more vitamins, and 30 to 45 per cent more protein than does the normal nonpregnant woman. Unless the proper selection of foods is made, her diet will result in too great an increase in weight but will at the same time be deficient in iron, proteins, and possibly vitamins. The woman who eats less during pregnancy than before almost surely will develop a deficiency. This is substantiated by the reports of Strauss,[1, 2] Tompkins,[3] and Arnell, et al.,[4, 5] which indicate that a protein deficiency edema is common during pregnancy. The high incidence of vitamin deficiencies and anemia in pregnancy is also well established.

The relationship of nutritional deficiencies to toxemias of pregnancy is sufficiently close to suggest to some observers, e.g., Ross,[6] Tompkins,[3] and Bibb,[7] that a nutritional deficiency may be a causative factor.

Certainly in pregnancy the physician should attempt to prevent the development of a nutritional deficiency as well as to correct any deficiency that already exists. This seems to be of particular importance in the patient with a toxemia. It is of interest that the microscopic evidence of liver damage in toxemias of pregnancy closely resembles that seen in livers injured by toxic agents such as chloroform and cinchophen. The importance of dietary protein as well as carbohydrate in protecting the liver against these toxins was noted by Davis and Whipple,[8] and has recently been given prominence by Ravdin,[9] Miller and Whipple,[10] Messinger and Hawkins,[11] and others.

The following report illustrates the important role played by nutritional therapy in a case of nephrotic toxemia of pregnancy.

Mrs. M. O'C., a graduate nurse, aged 22 years, was seen first at home on January 15, 1942, when she was approximately sixteen weeks pregnant. Her chief complaint was marked dyspnea, generalized edema, and weakness.

Her last menstrual period had occurred on September 3, 1941, and her expected date of confinement was June 10, 1942. Her illness began about December 1, 1941, when she was about two and a half months

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pregnant and under the care of her family physician. At that time she noticed increasing pallor, dyspnea on exertion, and swelling of the extremities. About December 25, 1941, edema was general, but it was marked over the buttocks and the extremities. Headache was constant. Treated with magnesium sulfate daily, Mrs. O'C. showed markedly decreased edema, and the headaches became less severe. On January 10, 1942, the edema increased, the headache became continuous, the pallor was marked, and dyspnea was worse, especially on exertion. A productive cough developed, and the sputum was occasionally blood streaked.

The patient gave a history of tonsillectomy and appendectomy in 1929, streptococcal sore throats in 1937 with no kidney nor heart complications that she was aware of, and rheumatic fever (six weeks in bed) in 1940.

On January 15, 1942, physical examination revealed marked pallor, a reddened injected pharynx, and a temperature of 100° F. The blood pressure was 178/112. The eye fundi were normal. The heart rate was 116 per minute, and the sounds irregular and of fair quality. Percussion revealed normal cardiac dullness. Presystolic and systolic murmurs were heard at the mitral area. Moist râles were heard in both lung bases with no areas of dullness in percussion. The liver edge was palpable and tender. A poorly-healed, right rectus scar was present. The uterus was enlarged to the level of a sixteen weeks' pregnancy. The urine gave a four-plus reaction for albumin, and showed 5 to 10 red blood cells, 20 to 30 white blood cells, and 3 to 4 hyaline casts to the high power field. Weight was 132 pounds, having increased 24 pounds since the onset of pregnancy, and edema was generalized.

A tentative diagnosis was made of rheumatic heart disease class III, streptococcal infection of the throat, and subacute glomerulonephritis complicating pregnancy of sixteen weeks' duration. Although the patient was referred for hospitalization, she remained at home. However, since throat irrigations and rest in bed produced no noticeable improvement in her condition, she was admitted to St. Vincent's Hospital, January 17, 1942.

Family history was negative. The history obtained from the training school confirmed the fact that she had had streptococcal sore throats in 1937. During the three years of training, urine analyses at three-month intervals had been negative. Blood chemistry examinations had been normal, and chest x-rays negative except that "the right hilus and left upper hilus show areas of calcified deposits suggestive of healed juvenile tuberculosis. The right diaphragm is irregularly raised due to adhesions, but there is no sign of active tuberculosis at this time." Her blood counts had been normal in every respect.

Following graduation from training school, the patient had rheumatic fever in September, 1940, and was confined to her home for six weeks. No laboratory data were available for this period. A report on chest x-rays taken in November, 1940 states "heart measures 12 plus cm. in the transverse axis. There is, however, a straightening of the left cardiac border which is frequently an early sign of mitral pathology. There is no evidence of recent lung parenchymal infiltration or pleural involvement." A clinical examination was made two months later (January 4, 1941), as follows: "Presystolic and systolic murmurs heard at the apex in the recumbent position. Left lateral prone position accentuates the presystolic murmur. The heart is not enlarged, rhythm is regular, and the rate is 72 per minute."

Diagnosis.—"Rheumatic heart disease. Mitral stenosis and mitral insufficiency Class I. Color poor. Patient is below normal weight, 102 pounds. Urine negative for albumin with negative microscopic examination." The electrocardiogram revealed at that time "right axis deviation and broad and bifid P-waves."

From the history given above it is evident that the attack of rheumatic fever had impaired the patient's heart valves to some degree, but at that time there was no evidence of involvement of the kidneys.

The patient was married in January, 1941, at the age of 21. She became pregnant and had a spontaneous abortion in April of that year when she was six weeks pregnant. Her history was then negative until her last period, September 3, 1941. Her progress up to admission to the hospital, January 17, 1942, has been given.

Upon entering the hospital the patient appeared acutely ill. Edema and pallor were marked, blood pressure was 144/96, temperature was normal. Presystolic and systolic murmurs could be heard at the mitral area, the liver edge was not palpable or tender, and the lung bases were clear. A catheterized specimen of urine gave a four-plus reaction for albumin. The specific gravity was 1.026. Microscopic examination of the urine showed 5 to 8 red blood cells, 20 to 25 white blood cells, and no casts per high power field.

Blood examination showed sedimentation time 26 minutes to 18 mm., 35 minutes to 26 mm.; hemoglobin 62 per cent; red blood count 2,600,000; white blood count 6,800 with differential count normal; Kahn test negative. The blood was type O.

On January 18, 1942, the urea clearance was 35 c.c. (100 per cent normal function). Chemical studies of the blood showed the following:

		NORMAL
Sugar	83	75 to 120
Uric acid	2.3	2 to 4
Urea N	11	10 to 20
Creatinine	1.5	1 to 1.5
Chlorides	554	380
Cholesterol	417	150 to 250
Albumin	0.96	3.8 to 6.0
Globulin	1.86	1.5 to 3.0
Total protein	2.82	6.3 to 8.0

The twenty-four-hour specimen of urine consisted of 880 c.c. (intake 1,000 c.c.) and contained albumin 11.5 Gm., with 10 to 15 red blood cells, 30 to 40 white blood cells, and occasional hyaline and granular casts per high power field.

Eye examination January 19, 1942, revealed the media clear, vessels A:V ratio 2:3. There was no exudate or hemorrhage.

The cardiologist reported as follows: "Patient is lying flat in bed with no respiratory distress. Vessels of the neck are not remarkable; thyroid isthmus is palpable. Heart by percussion normally situated; left border within normal limits. There is no thrill, heart sounds are of good quality. There is no notable accentuation of any of the base sounds. Over the pulmonic area there is a blowing systolic murmur. Rhythm is regular, rate 90, which slows markedly on vagus nerve stimulation. Edema of the face previously reported is not present now. Edema of the lower extremities and presacral area is marked. Impression: The subjective symptoms and signs are not due to cardiac failure. The physical examination does not reveal signs of chronic valvular disease. Electrocardiogram: Sinus arrhythmia."

TABLE I. INTRAVENOUS AMINO ACIDS IN NEPHROTIC TOXEMIA OF PREGNANCY

DATE	INFUSIONS	DIET (C 300, F 50)	AVERAGE TOTAL PROTEIN PER DAY	PLASMA PROTEIN GM./100 C.C.	HGB.	R.B.C.
Jan. 19 to Mar. 24	2,750 c.c. plasma 2,800 c.c. whole blood	P 160	165†	2.45 to 3.9	10.8 (62%)	3.01
Mar. 25 to May 3	45 Gm. amino acids/day*	P 100	145	3.8 to 4.8		
May 4, 5, 7, 8	90 Gm. amino acids/day	P 100	190	4.4 to 4.2	11.6 (68%)	3.36
May 6	400 c.c. whole blood	P 100	115†	4.4		
May 9 (Operation)	45 Gm. amino acids			4.1		
May 10 to 21	45 Gm. amino acids/day	P 100	145	4.8		
May 23 (Discharged)	650 c.c. whole blood	P 100	125†	4.8	11.3 (66%)	3.0
Oct. 13				6.44	14.3 (84%)	4.0

*6 days out of 7.

†Plasma calculated to contain 7% protein. Whole blood 54% plasma.

RENAL FINDINGS

DATE	UREA CLEARANCE	ALBUMINURIA QUAL.	ALBUMINURIA QUANT. GM./24 HR.	URINE C.C./24 HR.	WEIGHT LBS.
Jan. 19 to Mar. 24	54 c.c. (100%)	4+	7.5 to 12.5	450 to 1,000	132 increasing to 135
Mar. 25 to May 3		4+	8.3 to 14.2	1,000 to 2,250	135 decreasing to 126
Oct. 13	61 c.c. (110%)	3+	5.9	1,400	112

On January 20, 1942, x-ray of the chest showed "the heart measures 12½ cm. in the transverse axis. There is an increase, however, in the vertical diameter of the heart and recession of the aortic arch. These changes suggest enlargement of the right ventricle. The hilar densities and pulmonary markings are slightly increased. The apices, extreme peripheries, and lower angles are clear."

The patient was placed on a diet (Table I) consisting of 300 Gm. carbohydrate, 160 Gm. protein, and 50 Gm. fat. Vitamin, calcium and iron therapy was instituted, and vitamin C, 2 c.c. parenterally, was administered daily. The patient was extremely cooperative, and took her food *in toto* despite the fact that many times this required a great deal of effort.

On January 19, 1942, the patient was given a whole blood transfusion of 500 c.c. by the direct method. Another 500 c.c. whole blood transfusion was given on February 5, 250 c.c. on February 9, and 400 c.c. on February 12. Plasma transfusions (250 c.c.) were given on January 24, 27, and 29, and on February 3, 6, 9, 12, 18, 20, 24 and 28. After the first whole blood transfusion (January 19), the blood protein increased from 2.82 to 3.95, which was the highest point reached in spite of the high-protein diet, the 2,750 c.c. of plasma, and the 1,650 c.c. of whole blood given up to March 10.

The hemoglobin and red cell count steadily decreased, and on March 11, 13, and 17 a total of 1,150 c.c. of whole blood was given. This brought the total transfusions up to 2,800 c.c. of whole blood and 2,750 c.c. of plasma. No untoward reactions had been noted at any time from either the plasma or the whole blood transfusions.

The last three blood transfusions had brought the patient's total serum protein to 3.9 Gm. per 100 c.c. of blood. After rest in bed and the transfusions, the râles in the lung bases cleared, and the blood pressure dropped, varying between 130/70 and 106/64 during the patient's stay in the hospital. The edema was, however, still very marked especially in the dependent portions of her body. The total serum proteins fluctuated widely, and no real improvement could be noted in the patient's condition except for some slight improvement in the blood picture. There was still a good deal of doubt whether either she or the baby could survive.

On March 25, because of the patient's distaste for protein, her diet was changed. The carbohydrate and fat intake remained the same (C 300, F 50), but the protein was decreased from 160 to 100 Gm. per twenty-four hours and administration of amino acids solution was begun. Three hundred c.c. of 15 per cent amino acids solution (45 Gm. amino acids) were given every day from March 25 to April 29, inclusive, except on April 7, 13, 17, and 26. For the first three days the amino acids were given by mouth; thereafter they were administered intravenously. On April 30, after receiving 250 c.c. of amino acids solution, the patient experienced a moderately severe reaction, with chill, nausea, and epigastric pain. The intravenous solution was immediately stopped and none was given on May 1. Three hundred c.c. was given again on May 2 and 3, 600 c.c. on May 4, 5, 7, and 8, and 300 c.c. on the morning of the operation, May 9. Four hundred c.c. of whole blood was given on May 6 to combat the slight anemia.

After the administration of the amino acids was started, the serum proteins increased from 3.9 to a high of 4.8, then decreased to 4.4 and remained at that level, or slightly lower, until after her delivery by cesarean section, May 9, when the level rose to 4.8 Gm. per 100 c.c. of blood.

Clinically there was marked improvement after the amino acids were begun. The patient became more interested in her surroundings and very enthusiastic and cooperative. The edema, which had shown no noticeable change during the plasma and blood transfusions, decreased about forty per cent during the amino acids regime, and cleared entirely by the sixth day following delivery of the baby, except for slight ankle edema.

The daily urine analysis consistently showed a four-plus reaction for albumin. The red blood cells observed per high power field varied from 2 to 50, white blood cells from 10 to 100, and casts of the hyaline, granular, and cellular type were occasionally seen. A bi-weekly twenty-four-hour specimen showed 11 to 14 Gm. of protein per liter.

During the plasma and blood transfusions, fluid output varied between 500 and 900 c.c. per twenty-four hours, except on March 12, 14 and 18, when it was 1,160, 1,140, 1,100 c.c. on the three consecutive days following the whole blood transfusions. There was no noticeable increase in output following the plasma. Upon administration of the intravenous amino acids, the output was increased to a low of 1,680 c.c. and a high of 2,630 c.c. per twenty-four hours. On the days when the amino acids

were not given, the output varied between 585 c.c. and 860 c.c. per twenty-four hours.

On admission the patient weighed 132 pounds, a gain of 24 pounds since the onset of pregnancy. During the plasma and blood transfusion period her weight increased to 135 pounds, then decreased to 131 pounds. After the amino acids were begun, her weight decreased 5 pounds, so that on the day of operation the patient weighed 126 pounds.

Examination revealed the baby in transverse axis with the head on the left side and the face directed downward, with the cervix long, thick, and pointing high, forward, and toward the symphysis. Clinically the patient's pelvis showed a slight android tendency at the inlet but there was a satisfactory sacrosciatic notch and an average subpubic arch. X-ray confirmed these findings. The anteroposterior diameter of the inlet was calculated to be 9 cm. and the transverse diameter at the spines, 9.5 cm.

The findings given above were considered sufficient to warrant cesarean section rather than an attempt at induction from below. Accordingly, delivery was effected by low-flap section on May 9, 1942, under cyclopropane and oxygen anesthesia, the baby weighing 4 pounds, 15 ounces.

Convalescence was normal, with primary union of the wound. Forty-five Gm. of amino acids were given intravenously daily from May 10 through May 21. On May 23, when the patient was discharged from the hospital, she received 650 c.c. of whole blood. The baby was discharged on the twenty-eighth day after delivery, weighing 7 pounds, 5 ounces.

The patient was followed at monthly intervals after discharge. She seemed well, and was carrying on regular housework and caring for her baby. Monthly urine analyses gave a two- to three-plus reaction for albumin. Two twenty-four-hour specimens revealed 5 to 6 Gm. of protein per liter of urine.

On October 13, 1942, five months after delivery, the patient returned to the hospital for checkup. The values reported for chemical studies of the blood were as follows:

		NORMAL
Sugar	84	75 to 120
Uric acid	3	2 to 4
Urea N	9	10 to 20
Creatinine	1.2	1 to 1.5
Chlorides	515	380
Cholesterol	295	150 to 250
Albumin	3.71	3.8 to 6.0
Globulin	2.71	1.5 to 3.0
Total protein	6.44	6.3 to 8.0

Urea clearance was normal (110 per cent), but the urine still showed a high daily output of protein (5.9 Gm. per liter). The diet had been maintained at a high-protein level and included 45 grams of amino acids by mouth three times a week.

Discussion

Observation of the values reported for chemical studies of the blood upon admission of the patient shows that the blood sugar, uric acid and urea nitrogen are low-normal, probably an indication of a deficient diet, a failure to utilize ingested foods, or both. The creatinine is high-normal, but the cholesterol is markedly increased because of faulty metab-

olism. It can be seen that the albumin and globulin are decreased to a dangerous level. The protein loss through the urine has all but depleted the plasma albumin and has unbalanced the albumin : globulin ratio. Total protein is severely reduced.

A comparison of the results of chemical analyses of the blood upon admission with those reported five months after delivery, October 13, 1942, seems to point to improved nutrition due to supervision of the diet. The cholesterol, while still above normal, is markedly improved, as are also the albumin and globulin values.

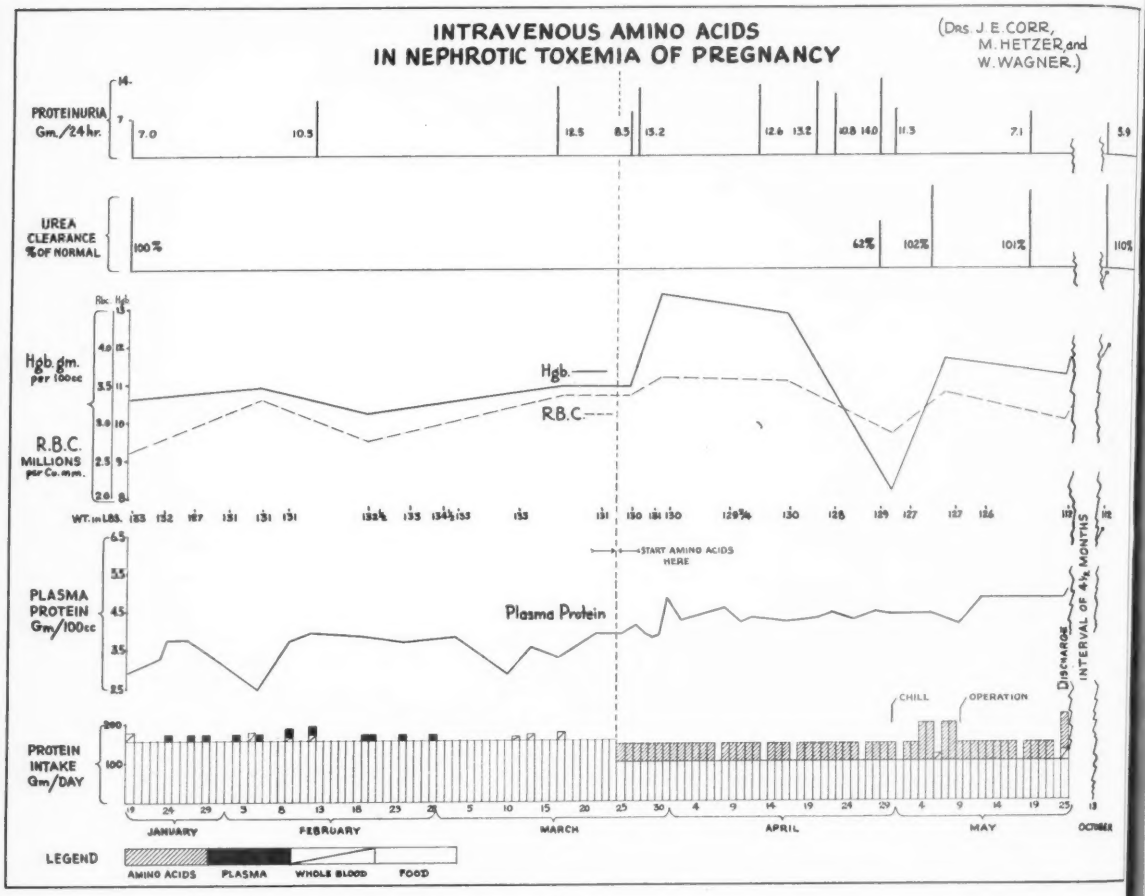

Fig. 1.

The graph (Fig. 1) divides itself very conveniently into two two-month periods, the first, from the date of admission January 17 to March 24; the second, from March 25 to the date of discharge, May 23, 1942. Each period represents a different form of therapy and a variation in the diet. Reading this graph from below upward, we note that the figures represent the daily protein intake, the plasma protein concentration, the patient's weight, the red blood cell count, the hemoglobin in grams, the urea clearance, and the proteinuria in grams per liter.

Plasma and whole blood have been converted to protein in grams on the basis that 7 per cent of plasma is protein and 54 per cent of whole blood is plasma. No allowance is made for the protein content of the red blood cells, for it has been repeatedly shown that they are not metabolized as protein when injected by vein. During this first period, when the basic diet contained 160 Gm. of protein daily, the protein derived from the transfusion of 2,750 c.c. of plasma and 2,800 c.c. of whole blood improved the protein intake to an insignificant degree. It produced a wide fluctuation of the plasma protein level and did not cause any sustained increase. This was doubtless due to the irregularity with which the whole blood was given, since the patient had to depend upon relatives and friends for procuring the blood.

In the same period it is seen that the weight decreased from 132 to 131 pounds. This represents a weight loss of one pound, but if we consider that in this period of two months the patient should have gained about five pounds in the normal course of her pregnancy, it is fair to assume that an actual loss of 6 pounds occurred which can be attributed to an extracellular fluid loss.

As this pregnancy advanced, the red blood cell count and hemoglobin estimation showed little change, the urea clearance varied slightly, and the proteinuria increased from 7 Gm. to 12.5 Gm. per twenty-four-hour urinary output.

The second period represents the amino acid regime. At this point, the patient began to tire of the high-protein diet, which was, therefore, reduced from 160 Gm. to 100 Gm. of protein daily, the grams of carbohydrate and fat remaining the same. To this diet was added 45 Gm. of amino acids daily. There occurred a dramatic increase in the red blood cell count. It is to be remembered that the patient had had iron therapy throughout her entire stay in the hospital. It is possible that at this point she formed an increased amount of hemoglobin because of the availability of globin derived from the amino acids, and, since the patient must have had adequate iron available, the iron may not have been the limiting factor. It is now believed that we do occasionally see protein deficiency anemias. These are, however, rare and represent only speculation on our part.

The plasma protein concentration definitely increased from an average of 3.5 to 4.8 Gm. per 100 c.c. of plasma. The postoperative increase is directly in line with the preoperative increase, and if the interval of four and one-half months between the date of discharge (May 23), and the date of readmission to the hospital for a checkup (October 13, 1942), were presented on another graph, the rate of increase in plasma concentration would be seen to be not too different from the rate of increase which occurred during the last two months of pregnancy.

The weight loss during this second period (131 to 126 pounds) is seen to be 5 pounds. Add to this the normal increase of 5 pounds as in the first two-month period, and we see a decrease in weight of 10 pounds.

The urea clearance and the proteinuria in this period show very little change over that of the first two-month period, except for about a week around April 28. At this point there is a marked fall in the hemoglobin and in the red blood cell count, an increase in the red blood cells in the urine, with a temporary decrease in kidney function, and a slower fall in the plasma proteins. We have attributed this to an acute exacerbation of the nephritis at that time. The increased output of albumin in the urine also suggests that the glomerulonephritis is still active.

The follow-up, five months after delivery, leads us to believe that the pregnancy did not aggravate the patient's nephritic condition. Here again we are speculating because of the lack of prepregnancy laboratory data. The continued presence of red blood cells and casts in the urine indicates a progressive nephritis, but would not the same picture present itself even though the patient had never been pregnant?

Conclusions

It is difficult to draw conclusions from the findings in this single case presentation, but we have been unable to find in the literature any similarly treated instance of pregnancy complicating a case of chronic glomerulonephritis with nephrotic syndrome. A more complete understanding of the chemistry of the body may, in the future, place an entirely different light on our present concept of nephritis. The clinical use of amino acids is apparently a step in this direction, for plasma and whole blood transfusions alone, or in combination with a high-protein diet, may not compensate for the protein loss through the urine in cases of nephritic and/or nephrotic toxemia of pregnancy.

We wish to express our thanks and appreciation to Frederick Stearns and Company of Detroit, Michigan, for their supply of amino acids; to Richard M. Johnson, M.D., for his invaluable help and advice in the treatment of this patient and in the preparation of this paper; and to Mr. Robert Bateman for assistance in the preparation of the graph.

Addenda

Since this case was reported on March 23, 1943, the patient was again successfully delivered of a living child, July 31, 1943. A brief review of her case seems warranted at this time.

Her diet when discharged in October 1942 after the checkup at the hospital, consisted of 200 Gm. carbohydrate, 100 Gm. protein and 50 Gm. fat with 45 Gm. of amino acids three times per week. Her last menstrual period was on November 15, 1942, with the expected date of confinement August 22, 1943. When seen on January 8, 1943, the patient's diet was reviewed, and a diet approximating 300 Gm. of carbohydrate, 100 Gm. of protein, and 50 Gm. of fat was suggested, and the amino acids were increased to 45 Gm. daily by mouth. The vitamin and iron therapy was slightly increased. The patient's weight was 112 pounds, the red blood cell count 4,240,000, hemoglobin 78 per cent of normal. Examination of the specimen of urine showed two-plus reaction for albumin, occasional hyaline casts, and no red blood cells. The eye grounds were normal. The uterus was slightly enlarged, in normal position, and movable.

The patient was seen at two-week intervals. Bimonthly twenty-four-hour specimens of urine were examined for albumin which revealed 3.7 to 4.2 Gm. The weight increase was gradual—112 pounds to 130 pounds on May 28, 1943. The blood pressure had varied between 112/58 and 122/68. The fetal heart was heard in the left lower quadrant.

At each examination the patient's ankles and calves were measured. Though not too accurate, this was an index of the nutritional edema as the pregnancy progressed.

ANKLE AND CALF MEASUREMENTS

Jan. 8, 1943	R.A.*	8 in.	R.C.*	12 in.	L.A.*	8 in.	L.C.*	12¼ in.
Feb. 10, 1943	R.A.	8 in.	R.C.	12¾ in.	L.A.	8¼ in.	L.C.	12¾ in.
Mar. 9, 1943	R.A.	8¼ in.	R.C.	13 in.	L.A.	8¼ in.	L.C.	13 in.
April 6, 1943	R.A.	8¼ in.	R.C.	12¾ in.	L.A.	8¼ in.	L.C.	13 in.
May 3, 1943	R.A.	8 in.	R.C.	12¾ in.	L.A.	8¼ in.	L.C.	12¾ in.
May 28, 1943	R.A.	8½ in.	R.C.	13¼ in.	L.A.	9 in.	L.C.	13¾ in.
June 25, 1943	R.A.	10½ in.	R.C.	15¼ in.	L.A.	10¾ in.	L.C.	16½ in.
July 2, 1943	R.A.	11¼ in.	R.C.	17¾ in.	L.A.	11¾ in.	L.C.	19¼ in.
July 14, 1943	R.A.	11 in.	R.C.	16¾ in.	L.A.	11½ in.	L.C.	18¾ in.
July 20, 1943	R.A.	11½ in.	R.C.	17¾ in.	L.A.	11¾ in.	L.C.	19¼ in.
July 27, 1943	R.A.	10 in.	R.C.	17 in.	L.A.	10½ in.	L.C.	18 in.
July 30, 1943	R.A.	9½ in.	R.C.	16¼ in.	L.A.	10½ in.	L.C.	16¾ in.
Aug. 10, 1943	R.A.	8 in.	R.C.	12 in.	L.A.	8¼ in.	L.C.	12½ in.

*R.A.—Right Ankle. R.C.—Right Calf.
L.A.—Left Ankle. L.C.—Left Calf.

On June 25, the patient's weight had increased to 139 pounds, and edema of the ankles, legs, sacral area and abdominal wall had increased markedly. By July 2, 1943, there was still further increase, and erythema of the palms of the hands was noted. Questioning of the patient resulted in an admission that her diet was not strictly adhered to as in the past and she stated that she had been unable to procure the amino acids solution. She felt well but the marked edema had interfered with activity. The blood pressure was 128/76 and the weight 147 pounds, an increase of 35 pounds since the onset of pregnancy and 17 pounds in the past five weeks (May 28 to July 2, 1943). A twenty-four-hour urine specimen revealed an output of 720 c.c., containing 15.2 Gm. of albumin, with occasional hyaline and finely granular casts, 1 to 2 red blood cells, and 2 to 5 white blood cells per high power field.

The patient was put to bed at home, her diet was reviewed again with her, and the amino acids solution was increased to four bottles (80 grams of amino acids) per day. The output of urine measured every twenty-four hours showed a variation from 1,120 c.c. to 1,960 c.c. up to July 14, 1943.

On July 19, 1943, when the patient was admitted to the hospital, her blood pressure was 138/80; but on the following day it was 110/56, and throughout her stay in the hospital it varied between 108/54 and 118/70. Her weight was 145 pounds, and, although edema was marked, there was no complaint. The fetal heart was in the left side, the fetus lying in transverse position, with the buttocks in the left iliac fossa.

The diet of C 300, P 100, and F 50 was continued but the amino acids were discontinued until the laboratory data were completed, July 23, 1943. On July 20, 1943, the red blood cell count was 3,460,000, hemoglobin 80 per cent of normal—11.6 Gm. Sedimentation time was 72 minutes to 16 mm. with urea clearance 58 per cent of normal. Urea content of urine 17. From July 19 to July 23 the daily urinary output varied from 430 c.c. to 1,140 c.c., and proteinuria from 9.8 to 17.2 Gm. per twenty-four hours, with 1 to 2 red blood cells, 2 to 4 white blood cells, and occasional hyaline and granular casts per high power field. The phenolsulfonphthalein test for the first hour was 200 c.c., 14 per cent; for the second, 250 c.c., 6 per cent.

Chemical studies of the blood and a comparison of the findings on January 18, 1942, when the patient was admitted to the hospital, with those of the date of

postoperative checkup, October 15, 1942, showed the following:

	JAN. 18, 1942	OCT. 15, 1942	JULY 20, 1943	AUG. 4, 1943	AUG. 12, 1943	NORMAL
Sugar	83	84	86	86		75 to 120
Uric acid	2.3	3	2.1	3.8		2 to 4
Urea N.	11	9	7	7		10 to 20
Creatinine	1.5	1.2	1.3	1.1		1 to 1.5
Chlorides	554	515	530	514		380
Cholesterol	417	295	433	378		150 to 250
Albumin	.96	3.71	2.7	2.6	1.93	3.8 to 6.0
Globulin	1.86	2.71	1.4	1.13	2.45	1.5 to 3.0
Total protein	2.82	6.44	4.1	3.73	4.38	6.3 to 8.0

Following collection of the above laboratory data, the diet of C 300, P 100, F 50 was supplemented by six bottles of amino acids (120 Gm. of amino acids) per twenty-four hours. This was continued until the day of discharge, August 11, 1943.

Twenty-four-hour urine specimens were collected twice a week from July 24, 1943, to July 31, 1943 (0.375 per cent to 5.5 Gm. albumin per twenty-four hours—0.345 per cent to 7.7 Gm.). The urinary output varied from 1,410 c.c. to 2,200 c.c. Measurement of the ankles and calves of the legs showed that edema decreased, though the patient was not kept in bed.

On July 31, 1943, a male child weighing 5 pounds, 8 ounces was delivered by low-flap cesarean section under cyclopropane anesthesia. The convalescence was uneventful, with primary union of the wound.

Postoperative urinary output varied between 1,960 c.c. and 2,460 c.c. (albumin 5.4 to 6.7 Gm.) per twenty-four hours. On August 5, 1943, the red blood cell count was 2,550,000, the white blood cell count 10,600, with hemoglobin 58 per cent of normal. Two transfusions of 500 c.c. whole blood each were given with the result that on August 11, 1943, the day of discharge, the patient's red blood cell count was 4,120,000 with hemoglobin 86 per cent of normal. The patient's weight was 114 pounds, and palmar erythema was still marked. The baby was discharged August 26, 1943, weighing 7 pounds, 4 ounces.

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THE COMPARATIVE VALUE OF ENDOMETRIAL BIOPSIES AND VAGINAL SMEARS*

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AMONG the methods now in vogue for estimating ovarian function and determining the effectiveness of hormonal therapy, two distinct groupings exist:

(1) The qualitative procedures, comprising the examination of vaginal smears, and the investigation of the endometrial pattern;
(2) The quantitative procedures, which include the hormonal assays of blood and urine.

The limited laboratory facilities for the latter and the incidental expense preclude the universal employment of hormone determinations for routine clinical and office work. Vaginal smears and endometrial biopsies, on the other hand, can easily be taken, not only for the diagnosis of ovarian failure, but also to determine the occurrence of ovulation. Particularly when sterility of endocrine origin is a problem, a knowledge of whether or not the patient ovulates is of great importance.

This communication is presented with the thought in mind of evaluating the clinical practicability and the advantages and disadvantages of the vaginal smear method, as compared with the study of the endometrial pattern.

Vaginal Smear Method

Using the morphologic changes occurring in the vaginal secretion as a criterion, Papanicolaou[1] demonstrated cyclic alterations in the vaginal mucus of women which were similar to smear changes, described by Stockard and himself,[2] in guinea pigs. Subsequently, Papanicolaou and Shorr[3] described the applicability of the vaginal smear method to the diagnosis of ovarian function and the objective evaluation of the effects of estrogenic therapy.

A small amount of secretion is obtained from the vagina by using a glass pipette fitted with a suction syringe or having a rubber bulb attached. The vaginal fluid is expressed on a clean slide and *immediately* immersed in a fixative—a mixture of equal parts of ether and 95 per cent ethyl alcohol. Staining of the slides according to one of the methods proposed by various investigators is then followed by a microscopic examination.

Our observations of the changes in the vaginal smears during the various phases of the normal menstrual cycle, on the whole, coincide

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with Rubinstein's description[4] of these alterations, which may be summarized as follows:

1. *Postmenstrual Phase.*—The follicle is commencing to develop, estrogen elaboration is at a low level and thus proliferation of the vaginal mucosa is only beginning. The epithelial cells in the smear exhibit predominantly large round vesicular nuclei and granular cytoplasm. In addition many leucocytes and bacteria as well as some thick mucus are present.

2. *Preovulatory Phase.*—As the immature follicle develops, the first peak of estrogen secretion is reached. Concurrently there is increase in proliferation of the vaginal mucosa which thickens. The superficial cells which at this stage are further away from their basal blood supply show more cornification. The nuclei of the epithelial cells become smaller, stain deeper and are pyknotic, the cytoplasm has lost its granular contents, is clear and the edges are distinctly defined. Bacteria and leucocytes gradually disappear from the picture.

3. *Ovulatory Phase.*—With follicle rupture there is a sudden decrease in estrogen secretion, which often is reflected by the appearance of some red blood cells in the smear. In addition, there is marked desquamation of cornified cells, there are very few leucocytes and bacteria, and there are some cornified cells with folded edges.

4. *Postovulatory Phase.*—This phase is dominated by a rapidly forming corpus luteum. Since both estrogen and progestogen are now secreted, proliferation and secretion of the vaginal epithelium is stimulated. The smears show continued desquamation of cells which are characteristically crumpled and folded together. Several types of epithelial cells are present. Some are completely cornified, the cytoplasm—wrinkled with scalloped edges—is agranular, while the nuclei are small and dense, fragmented or completely absent. Most frequently the nuclei are pyknotic but sometimes they may be vesicular. Other cells show large and oval nuclei with a wrinkled cytoplasm and scalloped edges; their cytoplasm is granular and occasionally vacuolated. This type is supposedly suggestive of progesterone activity. There is a marked influx of leucocytes and bacteria. The mucus remains abundant.

5. *Premenstrual Phase*—While progesterone elaboration increases, the smears show cells with larger, more vesicular nuclei. There is an abundance of leucocytes, bacteria and mucus. With the regression of the corpus luteum—accompanied by decrease of production of the ovarian hormones—the cells, which proliferated previously under the influence of estrogenic hormone, slough off and fragment. Their nuclei may be vesicular or pyknotic. The cells may be broken into halves with one part containing the nucleus. The cytoplasm may show partial cornification and granular vacuoles may be present. In addition, few red blood cells, many leucocytes and much mucus, many bacteria and much debris are present. The smear as a whole is termed 'dirty.'

6. *Menstrual Phase.*—The smear consists predominantly of blood and mucus. Since follicle stimulation by the anterior lobe of the pituitary begins anew during the bleeding phase of the cycle, the epithelial cells present reflect the earliest phase of follicular development.

Prima facie from the above it becomes clear that it is more difficult to evaluate the cytology of the vaginal secretion during the second half of the cycle.

Referring to Papanicolaou's description of the changes in a typical 28-day cycle, Mack[5] in his most comprehensive review states, "It is obvious, from the bizarre and varied cytologic patterns described, that more than ordinary microscopic skill and experience is necessary to conduct such investigations." Also in regard to Rubinstein's description it can be said that the proper interpretation of the cytologic appearance of the smear "is the province solely of the expert histologist."

The cytologic appearance of smears obtained from patients with estrogenic deficiency is more clear-cut. The atrophic changes characteristic of ovarian failure are readily recognizable, at least, in severe deficiency cases. There is a great number of round cells, which stain deeply, with large nuclei. Many leucocytes and usually bacteria are present and there is a lack of cornified epithelial cells. Symptomatic relief in estrogen deficiency cases produced by administration of follicular hormone is frequently associated with a transformation of the cytologic pattern of the smear to the type which is found during the proliferative phase of the normal menstrual cycle. However, we have also observed cases in which estrogenic therapy produced complete subsidence of clinical symptoms while the vaginal smear still showed a prevalence of atrophy cells. On the other hand, we observed occasionally transformation of the atrophy smear to complete cornification of the cells without correlation of these changes to symptomatic relief. The same observations were noted by Eisfelder[6] who, reporting on a series of more than 200 menopausal patients, states that the "vaginal smears may not always be a reliable index to therapeutic response."

The differential diagnosis between ovulatory and anovulatory bleeding is ofttimes of great importance and a practical technique not involving tissue removal and simpler than the determination of urinary pregnandiol complex as devised by Venning and Browne[7] would be of inestimable value. It has been our experience that the vaginal smear method certainly does not offer an ideal means for diagnosing ovulatory failure. However, when a number of cycles have been followed, in some instances we were able to establish a diagnosis of anovulatory menstruation. The preovulatory type of smear prevails for an unusually long period of time; no regression of the cells is observed as it is typical of the postovulatory phase and there is no premenstrual picture; the cells in the smear at the time when bleeding occurs show marked cornification. But certainly there might be a variance of opinion as to the applicability of the vaginal smear method for establishing the diagnosis of anovulatory bleeding in some cases. Shorr[8] considers it likely that the lack of uniformity in the appearance of the vaginal smear during the second half of the cycle results from the interaction of both ovarian hormones. "Any variation in the tempo or the extent of their production could be expected to vary the cytology of the vaginal secretion."

After reviewing the literature, Mack[5] concludes that "no confirmatory evidence of the value of vaginal smears for the detection of ovulation has as yet been produced."

From the foregoing discussion, it can be readily inferred that the study of vaginal smears as a diagnostic method has both advantages and disadvantages. Some of these are obvious while others become evident only after experience.

Among the advantages the following present themselves:

Ease of Collection.—There is no trauma or discomfort to the patient. There is no bleeding, and there are no aftereffects. The method is readily suited to the study of endocrine disorders in unmarried girls. The patient may collect the specimens herself and bring them to the doctor or laboratory at her convenience. The method permits of daily observations.

Absence of Risk.—There is no possibility of infection by introducing bacteria into the uterus, nor by lighting up latent adnexal disease. During a sterility investigation, a very early pregnancy might not be recognized by clinical observation. Obtaining smear specimens, the study of which might be revealing, will not lead to abortion.

Diagnostic Potentialities.—The method affords valuable information in cases of ovarian failure, particularly when there is severe estrogen deficiency. It is possible to check the response of the patient to estrogenic therapy at frequent intervals. Ofttimes the effect of treatment can be objectively proved in the smear—though vaginal cytology is not an absolutely reliable index for therapeutic response. Another advantage is that microscopic bleeding can be readily detected.

Among the disadvantages the following may be listed:

Difficulty of Interpretation.—Except in severe estrogenic deficiency cases, it is not possible to arrive at a definite conclusion based on this method alone unless one has given considerable time to the study of vaginal cytology. Even then, the method is not entirely dependable particularly so if it involves making a differential diagnosis of an ovulatory or an anovulatory cycle or determining the time of ovulation. There is an almost infinite gradation of types of cells and both the individual cell and the entire picture must be considered. Furthermore, the presence of infection modifies the smear. These changes are most striking in conditions such as cervicitis or vaginitis. No two cycles are exactly the same. The time of ovulation in some instances may be characterized by a leucocytic exodus; in others, this does not take place. In short, specialized training is a necessity, and the method is suited to the trained pathologist or to the physician especially interested in gynecologic endocrinology rather than to the general practitioner.

Time Element.—In most cases it is essential to study a series of slides throughout a menstrual cycle. To obtain the desired information, repeated observations are necessary, particularly if the presence or absence of ovulation is questionable.

Endometrial Biopsy

According to Herrell,[9] Westphalen,[10] who published his work in 1896, was probably the first to study the endometrium in relation to the menstrual cycle. Several years later Hitschmann and Adler[11] gave their classical description of the histologic changes occurring in the uterine mucosa. These investigators divided the human cycle into four stages: the postmenstrual phase, the interval phase, the premenstrual phase, and

the menstrual phase. Novak[12] in a recent work still adheres to the classification of the cyclic changes in the endometrium as proposed by Hitschmann and Adler. In the light of their findings and with the subsequent recognition of the relationship between endometrial changes and the function of the ovarian hormones, histologic investigations of the endometrium in bleeding disorders caused by endocrinopathies were greatly stimulated. For instance, the significance of endometrial hyperplasia in certain cases of metrorrhagia was clearly demonstrated. Also, much was learned about anovulatory cycles by means of endometrial biopsy.

The instrument we have been using to obtain endometrial biopsy specimens is a cannula curette as devised by Randall.[13] The tissue specimens are fixed in Buoin's solution embedded in paraffin, cut and mounted, and the sections stained for microscopic examination.

The following short, concise summary of the normal cyclic alterations in the endometrium bears repetition—it is based on the description of these changes as given by Campbell, et al.[14]

1. *Follicular Phase.*—The characteristic feature is cellular proliferation indicated by the presence of numerous mitotic figures in the stroma and especially in the glandular epithelium. The endometrium increases in thickness and vascularity and both stromal and glandular cells increase in size. The nuclei of the glands remain in contact with the bases of the cells. No glycogen or mucin is present. The lumina of the glands are round and regular, and there is a thin, albuminous secretion present. Early in the follicular phase the stroma is somewhat loose, but later on becomes progressively more dense. Toward the end of the follicular phase proliferation becomes much slower, mitotic figures are fewer and the glands present a somewhat wavy form upon longitudinal section.

2. *Luteal Phase.*—Here the first characteristic manifestation is the elevation of the nuclei from the bases of the cells of the glandular epithelium producing a conspicuous basal clear zone. This clear zone is filled with masses of glycogen which push the nuclei up toward the lumina. There is a rapid reduction in the number of mitotic figures and there are enlargement and pronounced elongation of the cells lining the endometrial glands. The entire endometrium becomes thicker during this period. However, this thickening does not keep pace with the increase in the size of the glands which results from enlargement of the secreting cells and dilatation of the glands with secretion. As a consequence, the glands become coiled and tortuous. The enlargement and crowding of the secretory cells produce the tuftlike protrusions into the gland lumen. The lumen on longitudinal section exhibits the typical sawtooth appearance. Coiling of the glands is most noticeable in the middle layers of the endometrium, their tortuosity becoming so great that the stroma cells are crowded out and are forced up toward the surface of the endometrium. This proliferation divides the endometrium into three distinct zones. The superficial zone (*Zona compacta*) is composed of relatively straight glands separated by masses of stroma cells. The middle zone (*Zona spongiosa*) is composed of many coiled glands with hardly any interstitial cells between them. The deepest layer of the endometrium (*Zona basalis*) is only slightly affected by the cyclic changes.

Late in the luteal phase the columnar cells which line the endometrial glands have now discharged most of their glycogen and appear shrunken and the lumina become even more ragged in outline. The endometrial arterioles assume a definitely spiral shape. Stroma cells of the compacta which have been gradually increasing in size now become definitely edematous, their fibrillar character has been entirely lost and their polygonal cell walls are now definitely seen. These cells have the characteristic decidual appearance, but this is not a true decidua. The presence of glycogen in the stromal cells which is a characteristic feature of true decidua is not observed. Finally, congestion and leucocytic infiltration herald the next menstruation period.

It becomes immediately evident from the above that the histologic characteristics of the endometrium during the second half of the normal cycle are as readily recognizable as those seen during the proliferative phase. However, the histologic appearance of biopsy specimens from patients with ovarian dysfunction is more varied. Among the abnormal endometrial patterns encountered by the clinician, and classified so carefully by Kotz and Parker,[15] most clearly defined are the atrophic and hyperplastic endometrium. In evaluating an endometrial specimen, it is very important to consider at which time of the cycle the biopsy was performed. For instance a normal structure occurring at the wrong time of the cycle is indicative of some pathology. It is generally agreed that a secretory endometrium reflects an essentially normal ovarian function, including the occurrence of ovulation; that atrophy of the endometrium, occurring in the menopause and in long-standing amenorrhea, is associated with severe ovarian failure; that a hyperplastic endometrium, usually accompanied by functional uterine bleeding, is an indication of an abnormally marked estrogen effect; and finally that a persistently follicular pattern of the endometrium just before the expected date of menstruation indicates absence of ovulation.

As with the vaginal smear, the study of endometrial biopsy specimens, as a diagnostic method, has both advantages and disadvantages. Among the advantages the following present themselves:

1. *Simplicity of Procedure.*—The actual operation of obtaining the biopsy specimens occupies only a short time. The technique when carried out under strictest aseptic precautions by a well-trained individual is safe, requiring only simple instruments, and very rarely anesthesia or hospitalization. It is feasible to study successive specimens which, as Hamblen[16] states, "permits an inference being drawn as to the approximate levels of ovarian function, as manifested spontaneously or as altered by therapy."

2. *Diagnostic Potentialities.*—The endometrium reflects the presence or absence of progesterone production and thus gives correct information regarding ovulation, the occurrence of which can be determined in most cases with a single specimen. Persistent anovulatory cycles may be easily diagnosed with several premenstrual biopsies during successive cycles.

Among the disadvantages may be listed:

1. *Risks Involved.*—Lighting up of a latent adnexal disease is possible, and the method is contraindicated in the presence of pelvic pathology. In any case, there is some discomfort to the patient and slight bleeding during and shortly after the procedure. Pregnancy, unless ruled out previously, may sometimes be interrupted when an endometrial biopsy is performed. In very early pregnancy this interruption may be inevitable.

2. *Shortcomings of Interpretation.*—The technique does not allow investigation of the entire endometrium. Thus the specimen obtained might not truly reflect the ovarian function because of the different histologic patterns sometimes present in various areas of the uterine cavity. Consequently, it is advisable that more than a single biopsy specimen be used for diagnostic purposes. Another shortcoming is that the exact time of ovulation cannot be determined.

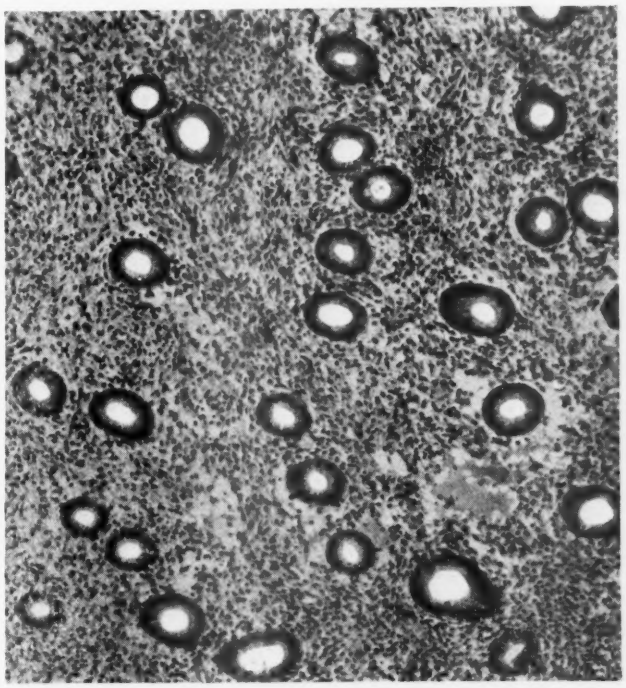

Fig. 1.—Midfollicular phase of endometrium, absence of any luteal change.

3. *Other Disadvantages.*—In virgins endometrial biopsies may be unobtainable. Finally, small areas of malignancy may be missed.

Of the many observations made in the course of this study, we are presenting only a few which will clearly exemplify the foregoing.

Patient C. consulted us because her marriage of several years' duration had remained barren. She stated she had menstruated regularly ever since her menarche at the age of 14. General physical and gynecologic examination, including the Rubin test, revealed no evidence of a pathologic condition. A semen analysis of the husband was satisfactory in every respect. It was attempted to corroborate a tentative diagnosis of anovulatory bleeding by both an endometrial biopsy and a vaginal smear. The endometrial biopsy (Fig. 1) taken two weeks after cessation of menstruation shows no attempt at a luteal phase. On the other hand,

the vaginal smear (Fig. 2) exhibiting many anuclear cornified cells may be interpreted as premenstrual. Occasional cornified cells, many leucocytes, and occasional red blood cells, might be interpreted as post-menstrual. It is very difficult to differentiate in this instance. Thus, the endometrial biopsy permits a clear-cut diagnosis of an anovulatory cycle while the single vaginal smear specimen does not throw light upon the problem.

Fig. 2.—Vaginal smear shows occasional cornified cells, anuclear cornified cells, many leucocytes, occasional red blood cells, and superficial cells. This smear does not illustrate any particular phase of a normal cycle.

Whether vaginal smear specimens or endometrial biopsies more clearly reflect corpus luteum hormone activity could be quite definitely shown in surgically castrated women, in whom any effects upon vaginal secretion and endometrium respectively are a mathematical function of any hormonal compounds previously administered. One of us[17] had shown that in human castrates the ingestion of estradiol and pregneninolone properly timed produced secretory changes of the endometrium. It was these experiments which we repeated for proper assessment of the present problem. Illustrative of these trials are the following cases:

Patient M. S., aged 33 years, had had no menses for 9 years following a bilateral salpingo-oophorcystectomy. Gynecologic examination revealed atrophic external genitalia with a small vaginal orifice. The cervix was atrophied and the retroflex uterus measured 2 inches from external os to fundus. Four mg. estradiol* daily were given for 12 days.

*The estradiol (Dimenformon) and pregneninolone (Progestoral) administered to these and all our other patients were kindly supplied by Dr. Pirk of the Roche-Organon Company.

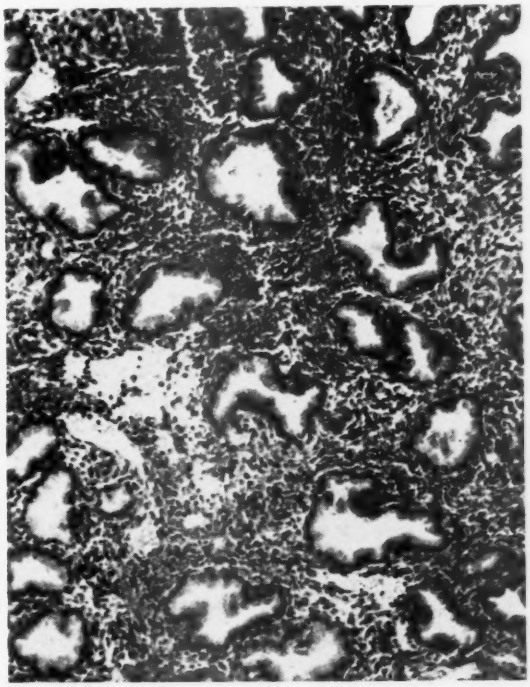

Fig. 3.—Human castrate. Late luteal phase of endometrium following dimenformon and pregneninolone medication.

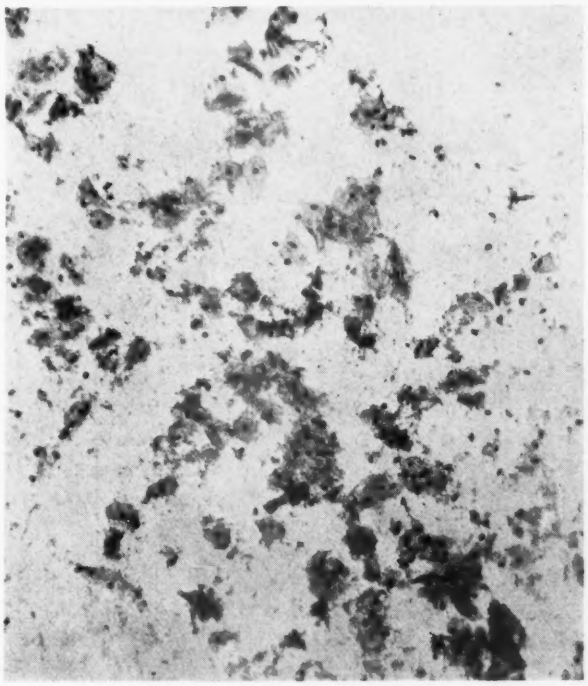

Fig. 4.—Vaginal smear shows insufficient action of estrogen, no cornification and is not indicative of any progestogenic influence.

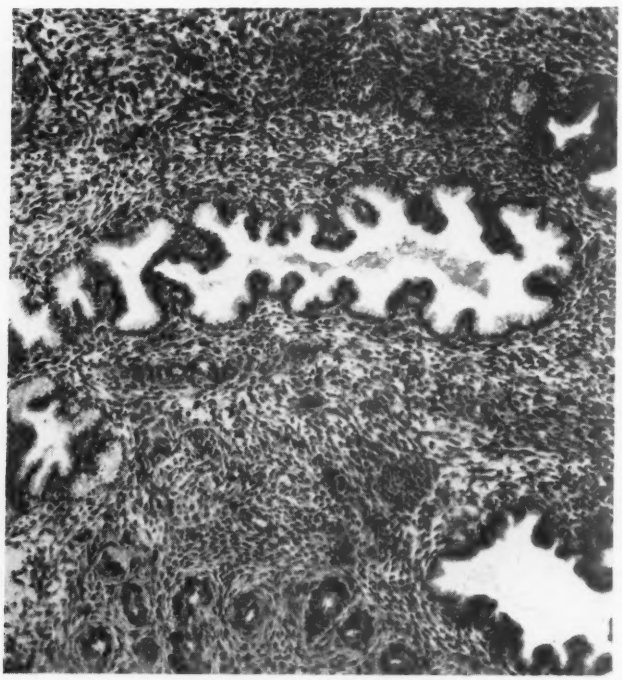

Fig. 5.—Human castrate. Good luteal phase of endometrium following dimenformon and pregneninolone medication.

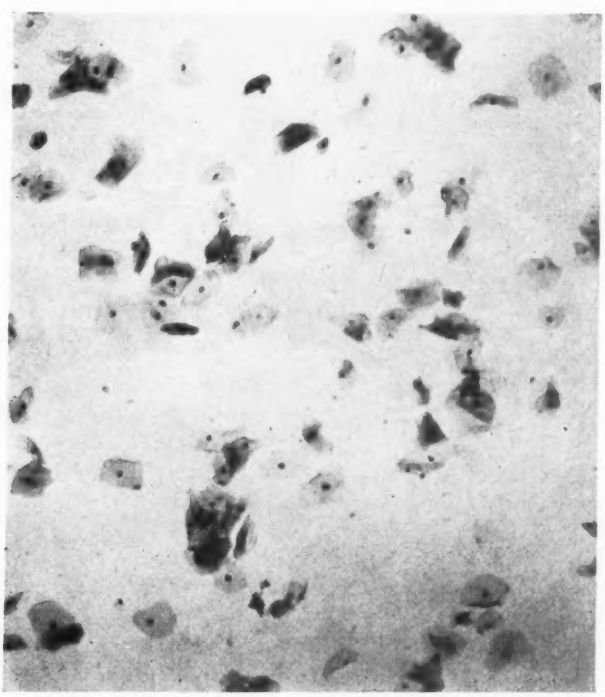

Fig. 6.—Vaginal smear shows groups of cornified cells and some superficial cells. This is considered good estrogenic action but no progestogenic influence.

This medication was followed by a dose of 6 mg. estradiol plus 100 mg. pregneninolone* daily for 12 days. Thus within 24 days a total of 120 mg. estradiol and 1,200 mg. pregneninolone was administered. While the premedication biopsy had revealed an atrophic endometrium, the post-medication biopsy (Fig. 3) shows a luteal phase clearly reflecting the previous hormone administration. Yet, the vaginal smear (Fig. 4) taken at the same time as the postmedication biopsy, shows insufficient action of estrogen, no cornification, and is not indicative of any progestogenic influence. This smear certainly is of no diagnostic value.

In another human castrate, R. M., with the usual menopausal symptoms, biopsy shows an atrophic endometrium and the vaginal smear corresponds to her estrogen deficiency state. There were many deep cells with pus, indicating menopause. Following administration of 120 mg. estradiol and 1,200 mg. pregneninolone, given as before outlined, biopsy reveals a fairly good luteal phase (Fig. 5) reflecting the use of progestogenic hormone. However, the vaginal smear specimen (Fig. 6) taken at the same time as the postmedication biopsy shows groups of cornified cells and some superficial cells. This is considered a fair amount of cornification but there is no indication of any corpus luteum action.

Summary

In summary then, for practical purposes the vaginal smear method, in most instances, will yield correct information regarding estrogen elaboration during the proliferative phase of the cycle. The technique is simpler than that of endometrial biopsy but particularly during the progestational phase it is ofttimes very difficult to evaluate the smear picture, to say the least. If information regarding progestogenic activity or ovulation is sought, the endometrium will serve as a reliable indicator. The vaginal smear, on the other hand, does not give any definite indication of corpus luteum action and thus no clue as to whether or not ovulation has taken place.

I wish to express my grateful appreciation to Dr. Walter T. Dannreuther for his kind assistance and efforts in making this work possible.

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Beruti, Josue A.: The Problem of Natal Mortality, Arch. Clin. obst. y ginec. "Eliseo Canton" **1**: 29, 1942.

Josue A. Beruti (Buenos Aires) in an introduction to a subsequent statistical study, discusses natal and neonatal mortality as factors involved in the declining birth rate in Argentina. Although infant mortality in general has decreased markedly, there has been an alarming increase in neonatal mortality. Twenty-five per cent of all infant deaths occur during the first three days of life. The author considers that stillbirths should also be included in a study of infant mortality and that gynecologists and obstetricians should be concerned with the possibility of reducing their incidence by more intensive application of the principles of hygiene, preventive medicine, obstetrics and pediatrics. Because of varying definitions of natal mortality, official statistics on the subject are hopelessly confused. In Buenos Aires a lapse of three days is allowed between birth and registration, thus death of a child within this time is recorded as a stillbirth. The author defines the categories which he uses in his statistical study. A viable child born without heartbeats is considered a stillbirth; a child of less than 2,500 Gm. is called premature; "newborn" includes birth to one month.

According to statistics published in the bulletin of the Panamerican Health Office, Feb. 1, 1940, there are few American (N. and S.) countries and cities which have shown a regular and continued decrease in natal mortality, many of which have shown an increase and most showing no definite increase or decrease. Statistics for Buenos Aires (Municipal Statistical Review) during the period 1914 to 1939 shows in general a descending tendency (maximum 1923, 5.3 per cent, and minimum 1939, 2.6 per cent). The decrease is almost constant since 1927 and absolutely constant since 1934. According to De Rudder, the neonatal mortality of the world has increased slightly.

Different laws and customs governing registration of births, differing criteria for determining stillbirths and laxity in reporting births contribute to inaccuracy even in official statistics. In hospitals, especially children's hospitals and maternity centers, the more careful records and better discrimination as to the causes of fetal or infantile deaths make statistics from such sources more valuable, but with its accumulation of complicated cases a hospital does not adequately represent a province or locality. For this reason the statistics which the author is to present, although based on a great number of cases, represent a particular situation. A more complete picture could only be obtained by combining statistics from all maternity centers of all cities and towns in the Republic. Since this is at present Utopian, he confines himself to an investigation of the clinical material from one maternity center in Buenos Aires, hoping that this combined with material from other institutions may yield some instructive facts. The author warns that the statistics are not absolutely perfect since the clinical records, especially in early years, are not all satisfactory and since diagnostic, prophylactic and therapeutic criteria have not remained constant through the years.

J. P. Greenhill.

DEMEROL (S-140) AND SCOPOLAMINE IN LABOR

A Study of 1,000 Cases

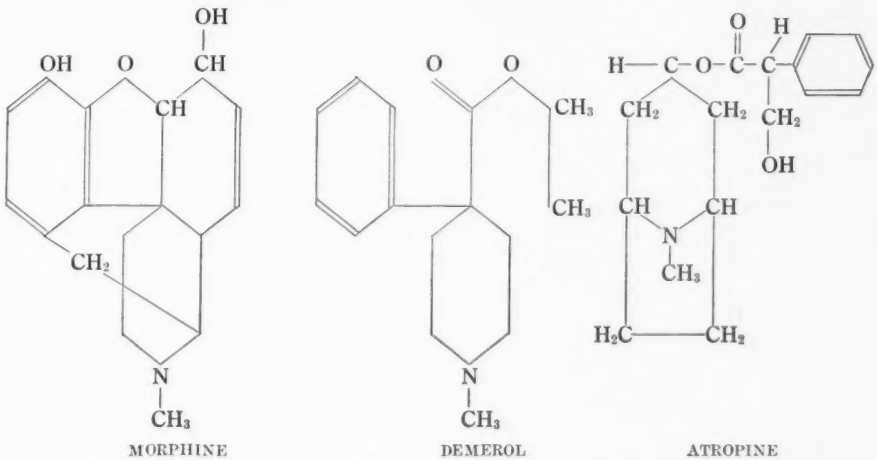
WILLIAM R. SCHUMANN, M.D., BOSTON, MASS.

(From the Department of Obstetrics, Harvard Medical School and the Boston Lying-in Hospital)

SINCE the practice of administering analgesic drugs in labor was begun at the Boston Lying-in Hospital in 1931, a constant effort has been made to find a medication routine which would afford complete amnesia for the mother, yet would produce no untoward effects in either mother or baby. Because we believe scopolamine to be the amnesic drug of choice, it has been incorporated in our medication routine. The adjuvant, be it morphine, barbiturate, paraldehyde, or Demerol, is used for its contributory soporific or analgesic effect. The psychic sedation obtained thus provides a favorable background for the action of scopolamine, reducing the excitement and enhancing the amnesia. Because the drugs commonly employed at present for this purpose are not ideal, Roby and Schumann[1] initiated the clinical study of Demerol* in conjunction with scopolamine as an obstetric analgesic at this clinic. It is the purpose of this paper to report the completion of our studies on one thousand cases.

Material

Demerol (1-methyl-4-phenylpiperidine-4-carbonic acid ethyl ester) was first described in 1939 by Eisleb and Schaumann[2] under the proprietary name Dolantin. It is a synthetic which exhibits properties analogous to both the atropine and morphine series (Schaumann,[3] Duguid and Heathcote,[4] Gruber, et al.,[5] Barlow and Hamburger,[6] Batterman[7]), although much weaker than atropine as a spasmolytic agent, and displaying properties midway between codeine and morphine as an analgesic. It differs from morphine in that it relaxes smooth muscle rather than causes spasm.



*The Demerol used in this study was generously supplied by the Winthrop Chemical Company, New York, N. Y.

The appealing property from an obstetric standpoint is the apparent absence of any significant narcotic depressant action, both in experimental (Schaumann,[3] Barlow and Hamburger,[6] Gruber, et al.,[5] Duguid and Heathcote[4]) and clinical (Batterman[7], Gilbert and Dixon,[8] Rovenstine and Batterman,[9] Roby and Schumann[1]) studies.

Demerol has no demonstrable effect on either the urine or blood picture (Hecht[10]). Batterman[7] reports a loss of gut motility in 84 per cent of patients studied, abolition of corneal reflex in 80 per cent, and no cases of primary addiction. Studies made by Himmelsbach[11] suggest that the risk of addiction would be negligible in doses employed obstetrically.

Side effects have been reported by several observers (Hecht,[10] Meyer,[12] Barlow, et al.,[6] Gilbert and Dixon,[8] Davis[13]), Batterman[7] finding the incidence to be 25.5 per cent in his hospitalized patients. He notes such effects in order of frequency as dizziness, nausea, pallor, diaphoresis, and dryness of the mouth. Respiratory depression was noted in only two markedly debilitated patients out of 774 cases. There is agreement that intravenous administration is attended by a higher incidence of side effects (Davis,[13] Meyer[12]), and Meyer[12] has tentatively concluded that intravenous administration may be hazardous. Following a 100 mg. dose to control hiccough, he observed profuse perspiration, nausea, emesis, temporary loss of consciousness, a rapid, thready pulse, and irregular respiration.

Method

Discrepancies in dosage and frequency of medication are inevitable when analgesia is ordered as needed by the house-officer on duty. To avoid such inequalities, a routine of medication was adopted for purpose of this study. All patients admitted to the hospital in labor were thereby insured identical medication, given at stated intervals. Although more practical on a busy service with two daily shifts of house-officers, this method has the disadvantage of inflexibility; no adjustment in dosage can be made for variations in body weight and rate of metabolism. Standing medication orders were as follows:

Routine medication:

(Unless otherwise stated, all medication is given intramuscularly.)

Initial medication:

Demerol 100 mg. Scopolamine gr. 1/100	Given when patient begins to mind her pains.
Scopolamine gr. 1/150	Given 45 minutes later.

Second medication:

Demerol 100 mg. Scopolamine gr. 1/200	Given 4 hours after first medication.

Subsequent medication:

Demerol 100 gm.	Given every 4 hours.
Scopolamine gr. 1/200	Given every 3 hours.

New admissions expected to deliver within 2 hours:

Initial medication:

Demerol 50 mg. Scopolamine gr. 1/200	*Slow* intravenous administration on admission.
Demerol 50 mg. Scopolamine gr. 1/200	Intramuscular administration on admission.

Subsequent medication to be given as per routine above.

Premedication for cesarean sections:

Demerol 50 mg. Scopolamine gr. 1/200	Intravenously	Given 45 minutes prior to anesthetic induction.
Demerol 50 mg. Scopolamine gr. 1/200	Intramuscularly	

The following alterations in routine were instituted during the course of the study as we became more familiar with the action of the drug:

Routine medication:

Subsequent scopolamine medication (gr. 1/200) was given at 2- instead of 3-hour intervals.

New admissions expected to deliver within 2 hours:

Demerol 100 mg.
Scopolamine gr. 1/100 — Slow intravenous administration on admission. Minimal 2 minutes for 2 c.c. 100 mg.

Premedication for cesarean sections:

Demerol 100 mg.
Scopolamine gr. 1/100 — Slow intravenous administration 45 minutes prior to induction.

Standing Nursing Orders:

1. Prior to initial medication, patient is urged to void, and canvas bedsides are placed on bed. Dentures are removed.
2. On administering initial medication, patient is told that she is receiving the medicine which will put her to sleep and prevent her feeling more pain.
3. No further conversation is held with patient.
4. Any deviation from routine of medication must be checked by resident physician before medication is given to patient.

Evaluation

Amnesia.—Each patient was interviewed the day following her delivery. She was requested to relate everything she could remember after receiving the initial medication, and leading questions were avoided.

The first 112 cases were interviewed by one examiner (Roby). Of the remaining 898 cases, 676 were interviewed by one examiner (W. R. S.), while 222 were seen by a third examiner (M. A.). This restriction on the number of examiners was made in an effort to minimize subjective variations in appraisal. The following arbitrary classification of amnesia was adopted:

1. Absolute amnesia.
2. Patient able to recall isolated incidents (being moved from labor room to delivery room, being moved from bed to delivery table, and having anesthetic mask applied), but recalling neither orderly sequence nor pain.
3. Patient able to recall a number of incidents in orderly sequence, but remembering little or no pain. In effect, poor amnesia but satisfactory analgesia.
4. Failure of amnesia or analgesia.

Effect on Newborn Infant.—To evaluate the immediate depressant effect on the newborn infant, the following arbitrary classification was adopted:

A. Infant breathes spontaneously with no resuscitation other than routine inversion and aspiration of upper airway with rubber ear syringe.
B. Infant requires administration of oxygen and/or warm bucket, but respires spontaneously within 2 minutes.
C. Infant requires more than 2 minutes of resuscitation before breathing spontaneously. Also any infant whose condition following delivery merits observation by the pediatrician.

Evaluation of persistent damage to the newborn infant is tabulated from the pediatrician's discharge examination on all "C" babies.

Maternal Effects

Amnesia.—The initial 112 cases have been previously reported (Roby and Schumann[1]) as "Good" and "Poor" amnesia as shown in Table I. Because "Good" embraces groups 1 and 2, while "Poor" includes groups 3 and 4, these original cases will not be included in the analysis.

TABLE I. SHOWING AMNESIA IN ORIGINAL 112 CASES (ROBY AND SCHUMANN[1])

AMNESIA	NUMBER OF CASES	PERCENTAGE
Good	97	84.8
Poor	15	15.2

Seventeen cesarean sections will be considered under separate head, and 34 cases have been discarded because they were prematurely medicated and subsequently permitted to come out of their analgesia. There remain 847 cases (Table II), in which it is seen that groups 1 and 2 (entirely satisfactory), comprise 70.5 per cent of the series.

TABLE II. SHOWING AMNESIA IN SUBSEQUENT 847 CASES

AMNESIA	NUMBER OF CASES	PERCENTAGE	
1. (Absolute amnesia)	286	33.8	70.5
2. (Isolated incidents)	311	36.7	
3. (Analgesia but no amnesia)	143	16.9	
4. (Failure of amnesia)	107	12.6	

In examining groups 3 (analgesia but no amnesia) and 4 (failure of amnesia), it became apparent that a number of cases had received medication too late to benefit materially from its effects, while a few had not been medicated as frequently as called for in the routine. If the fault in these cases be thought to lie in the administration rather than in the drug itself, then the corrected failure groups of 43 in group 3 and 38 in group 4 are seen to comprise 5.1 per cent and 4.5 per cent respectively of the entire group, or a total of 9.6 per cent.

TABLE III. SHOWING RELATION OF DURATION OF MEDICATION TO AMNESIA

GROUP 3 (GOOD ANALGESIA WITHOUT AMNESIA)	
Initial dose within 1 hr. of delivery	48
Initial dose within 2 hr. of delivery	37
Excessive interval between doses	6
Unqualified failure of amnesia	43

GROUP 4 (COMPLETE FAILURE)	
Initial dose within 1 hr. of delivery	55
Initial dose within 2 hr. of delivery	24
Excessive interval between doses	2
Unqualified failure	38

These figures are found to compare favorably with the extensive barbiturate-scopolamine series studied previously in this hospital (Irving et al.[13]), in which pentobarbital-scopolamine yielded an 86 per cent satisfactory amnesia.

Effect on Length of Labor

It is our impression that data on duration of labor need be regarded with reservation, for it is indeed difficult to appraise accurately the time of onset of labor. The following data are presented for comparison with other series. Curiously enough, the figures closely approximate those of Gilbert and Dixon,[8] who used demerol in conjunction with barbiturates, and who noted an average primiparous labor of 11.8 hours,

TABLE IV. SHOWING AVERAGE LENGTH OF LABOR

	PRIMIPARA	MULTIPARA
Total labor	12.4 hr.	7.6 hr.
First stage	10.6 hr.	6.8 hr.
Second stage	1.8 hr.	.8 hr.

an average multiparous labor of 7.1 hours. Rathbun,[15] in reviewing a series of 500 cases delivered under barbiturate-scopolamine analgesia at this hospital, found the average primiparous labor to be 14.9 hours, the average multiparous labor to be 8.8 hours. Thus, under the demerol routine, the average primiparous labor has seemingly been reduced by 2.5 hours, and the multiparous labor by 1.2 hours. This represents a 17 per cent and 14 per cent reduction, respectively, which would appear to be significant.

Preanesthetic Effect

No statistics have been collected on anesthetic complications of induction in this series, but it is the opinion of the Director of Anesthesia (Hershenson[16]) that demerol-scopolamine as given in this routine is not surpassed by other preanesthetic combinations in common use at present. There have been no major pulmonary anesthetic complications in the series, and we have enjoyed complete freedom from the pulmonary edema crises seen occasionally with barbiturates.

In order to gain an approximate estimate of what effect, if any, demerol might exert on the quantity of anesthetic agent required, the amount of anesthetic agent used was carefully measured on 18 uncomplicated pelvic deliveries in the demerol series. For comparison, the same observations were made on 19 uncomplicated pelvic deliveries where the patients had received seconal gr. 3, sodium amytal gr. 6, and scopolamine gr. 1/100. All anesthetics were administered by the Di-

TABLE V. SHOWING AMOUNT OF ANESTHETIC AGENT REQUIRED

CARBON DIOXIDE ABSORPTION METHOD			
ANALGESIA	NUMBER OF CASES	AVERAGE AMT. VINETHENE	AVERAGE AMT. ETHER
Demerol-scopolamine	10	25 c.c.	20 c.c.
Seconal-Na amytal-scopolamine	13	26 c.c.	23 c.c.
OPEN DROP METHOD			
ANALGESIA	NUMBER OF CASES	AVERAGE AMT. VINETHENE	AVERAGE AMT. ETHER
Demerol-scopolamine	8	18 c.c.	91 c.c.
Seconal-Na amytal-scopolamine	6	19 c.c.	75 c.c.

rector of Anesthesia. The above data (Table V) show little significant variation in the amount of anesthetic agent required in each group, and suggest that demerol and the barbiturates are equivalent in preanesthetic value.

Intravenous Use

The multipara admitted in active labor has heretofore presented a problem in obstetric analgesia. She frequently vomits oral medication and expels rectal medication, and even though she retains it, is usually delivered before the therapy becomes effective. Such difficulties led us to investigate the intravenous use of demerol-scopolamine analgesia. With our first 107 cases, we employed only half the initial dose intravenously, giving the remainder intramuscularly. When it became apparent that intravenous administration was not hazardous, we gave the entire initial dose intravenously with improved amnesic results, as may be seen in Table VI. That these results were obtained in patients who would have shown little response to oral or rectal medication is emphasized by Table VII. Here it is noted that 64 per cent of the 50 mg. group and 62 per cent of the 100 mg. group were medicated for less than one hour.

TABLE VI. SHOWING AMNESIC EFFECT WITH INTRAVENOUS MEDICATION

DOSE EMPLOYED	AMNESIA CLASSIFICATION								(NO. OF CASES) TOTAL
	1	%	2	%	3	%	4	%	
50 mg. IM-50 mg. IV	28	26	39	36	28	26	12	12	107
100 mg. IV	6	21	16	55	5	18	2	6	29

TABLE VII. SHOWING LENGTH OF TIME ELAPSED FROM MEDICATION TO DELIVERY

DOSE EMPLOYED	NO. OF CASES					TOTAL
	1 TO 15 MINUTES	16 TO 30 MINUTES	31 TO 45 MINUTES	46 TO 60 MINUTES	OVER 1 HOUR	
50 mg. IV-50 mg. IM	8	17	4	29	49	107
100 mg. IV	5	9	2	2	11	29

Untoward Effects

The only unpleasant side effects noted in this series were in the patients receiving intravenous medication. With the exception of vomiting, no further untoward results were seen after we learned to give the drug slowly, taking at least two minutes by the clock to administer 2 c.c. (100 mg.). If the demerol-scopolamine mixture is given rapidly, the patient invariably vomits immediately, and over a transient 30 to 40 seconds, the pulse becomes rapid, irregular, and thready, with a gradual return to normal. The patient will ordinarily vomit two to three times before becoming drowsy, listless, and quiet.

If the drug is given slowly, about one-fourth of the patients will experience transient nausea, and may or may not vomit. If vomiting occurs, it is usually only once. The customary course is a pleasant sensation of warmth and euphoria, and a number of patients have felt as though they were floating up from the mattress. The patient next experiences a feeling of numbness, as though the whole body had "gone to sleep," and becomes quiet. She may respond lucidly to questions, but shows an increasing disinclination to respond, until finally she becomes disoriented in her response. From this point on, if adequate dosage is maintained, the patient will ordinarily sleep quietly between her pains. During a pain, she may rouse, attempt to move about or sit up in bed, mumble or cry out, and then relapse into quiet sleep when the pain has passed.

We have been unable to keep an accurate record of the incidence of excitement. It is our impression that a manic state occurs with about the same frequency as in barbiturate-scopolamine analgesia, and we believe that such excitement is the result of scopolamine idiosyncrasy, rather than an effect of the adjuvant, be it barbiturate or demerol. In general, however, the labor room has been noticeably quieter since the demerol routine supplanted both barbiturate and paraldehyde analgesia.

For the obstetrician accustomed to the use of barbiturates, we should like to include the observation that the demerol-scopolamine patient, even though adequately medicated, may respond to questions with a disconcerting lucidity. If, however, a medication routine similar to that used in this series has been adhered to, the amnesic result will be found comparable to that obtained with barbiturates.

Analgesic Effect

During a process such as labor, it would seem to be pharmacologically sound to use a true analgesic drug in conjunction with scopolamine if we are attempting to suppress the ascent of pain impulse to the level of consciousness. That demerol exerts a gratifying analgesic effect may be seen in Table VIII, which represents a group of 37 patients who

TABLE VIII. SHOWING ANALGESIA IN ABSENCE OF ANESTHESIA

Complete amnesia	9
Isolated incidents	10
No amnesia but no pain	10
Pain during delivery	8
Total	37

precipitated without anesthesia. Of these, 29, or 79 per cent, were delivered with no recollection of pain whatever, in spite of the fact that several patients sustained lacerations requiring repair.

Effect on the Newborn Infant

In the original 112 cases, Roby and Schumann[1] reported 16 slow babies. To permit a more detailed analysis, we shall present data on the remaining 897 cases, using the criteria previously described.

TABLE IX. SHOWING INCIDENCE OF FETAL MORBIDITY AND MORTALITY

CLASSIFICATION	NUMBER	PERCENTAGE
A (Active)	737	82.15
B (Slightly slow)	107	11.99
C (Slow)	30	3.3
Neonatal deaths	6	0.66
Stillborn	17	1.9

All of the babies in the B (slightly slow) group were normal on leaving the delivery floor and required no further attention. Of the thirty C (slow babies), 28 were discharged with the mother as normal, showing no demonstrable sequelae. Two were discharged for further follow-up with a diagnosis of severe asphyxia and cerebral damage.

It may be noted from the following protocol that with the exception of four babies, there is an adequate obstetrical explanation for the slowness of the newborn infant. Of the four slow babies following an uneventful labor and delivery, all were discharged as normal with the mother.

It will be noted from the foregoing protocols that each of the stillborns and neonatal deaths is readily explainable on the basis of con-

PROTOCOL I. SHOWING DISPOSITION OF C (SLOW) BABIES

	DISCHARGED AS NORMAL
97253	Mid transverse arrest. Pituitrin stimulation. Easy delivery.
97292	Seventeen-hour first stage. Two-hour second stage.
97299	Uneventful delivery. Observation only 2 days.
97327	Seventeen-hour first stage. Two-hour second stage. Fetal distress.
97427	Five pounds. Discharged from premature nursery on seventh day.
97434	Twin No. 2. Primiparous breech, forceps to aftercoming head.
97508	Persistent posterior. Manual rotation and low forceps.
97520	Uneventful delivery.
97534	Four and three-quarter-hour second stage with subsequent cesarean section for cephalopelvic disproportion.
97581	One-hour second stage with fetal distress.
97661	Secondary uterine inertia. Pituitrin stimulation.
97702	Mid transverse arrest with Barton forceps extraction.
97807	Uneventful delivery.
98068	Cord tightly about neck 1 ×. Overnight observation only.
98119	Low forceps for outlet arrest. Overnight observation only.
98127	Secondary uterine inertia with pituitrin stimulation.
98181	Primiparous breech with forceps to aftercoming head.
98208	Manual flexion of multiparous face presentation.
98230	Uneventful delivery.
98311	Fetal distress. Cord about neck 1 ×.
98334	Placenta previa.
98592	Manual rotation for persistent posterior. Low forceps.
98744	Uneventful delivery. Forceps abrasion to cheeks only.
99727	Manual rotation for persistent posterior. Low forceps.
99732	Fetal distress. True knot in cord.
99847	Fulminating pre-eclampsia, grade II, on veratrone with induction of labor by rupture of membranes.
100476	Mid transverse arrest with difficult forceps extraction.
	DISCHARGED AS ABNORMAL
97669	Manual rotation and low forceps for outlet contraction. Cephalhematoma and marked hyperactivity. Diagnosis—severe asphyxia with possible cerebral damage.
97754	Eleven-hour labor with 1½-hour second stage. Persistent midtransverse arrest with manual rotation and midforceps extraction. Discharged from observation on twenty-first day with diagnosis of severe asphyxia and cerebral damage.

PROTOCOL II. STILLBORN

97182	Anencephalic.
97281	Extensive intracranial hemorrhage. Liver 2 × normal.
97625	Monster with multiple congenital abnormalities.
97644	Erythroblastosis.
97799	Dead on admission.
97828	Macerated 2-pound infant.
97896	Anencephalic.
97995	Erythroblastosis.
98066	Dead on admission. Cord 3 × about neck.
98122	Fetal heart disappeared 38 minutes before delivery. Cord 1 × tightly about neck.
98148	Hydrocephalus and spina bifida.
98265	Erythroblastosis.
99740	Two-pound 5-ounce primiparous breech.
99860	Probable erythroblastosis.
100221	Diabetic mother. Dead on admission.
100399	Four-pound 8-ounce twin No. 1. Pre-eclampsia, grade II.
100532	Dead on admission.

PROTOCOL III. NEONATAL DEATHS

97467	Died fourth day massive intracranial hemorrhage.
97849	Died third day intracranial hemorrhage. Mid transverse arrest with difficult forceps delivery.
98574	Died 10 minutes multiple congenital anomalies.
100504	Died 12 hours. Tumultuous 4-hour primiparous labor.
100646	Died 2 hours. Erythroblastosis.
100739	Died 48 hours congenital heart.

genital deformity or pathological state, and it would therefore seem that there is no need to implicate the maternal analgesia as an etiological factor.

Premature Infants

Realizing that any depressant action of obstetrical analgesia on the newborn would be maximal in the premature group, the following analysis of the premature infants in the series is presented.

PROTOCOL IV. SHOWING CONDITION OF 44 PREMATURES

CONDITION	WEIGHT		REMARKS
	POUNDS	OUNCES	
A	5	8	
A	4	¼	
A	6	6¼	Twin #1
A	5	12	Twin #2
A	5	5	
A	4	9	
A	5	0	
A	5	5½	
A	5	9	IV 50 mg.—IM 50 mg.
A	1	0	Died 12 hours of prematurity.
A	5	5	
A	4	15½	IV 50 mg.—IM 50 mg.
A	4	10	Twin #1
A	5	0	Twin #2
A	5	13¾	Twin #1
A	5	14¼	Twin #2
A	6	11	Twin #1
A	7	5	Twin #2
A	4	14	Twin #1
A	5	½	Twin #2
A	5	12	Twin #2
A	5	3¼	
A	5	4	
A	3	0	Twin #2
A	5	9	IV 50 mg.—IM 50 mg.
A	5	12	Twin #2
A	3	12	
A	2	13	Twin #1
A	2	14	Twin #2
A	6	10	
A	4	2	IV 50 mg.—IM 50 mg.
A	3	5	Twin #1
A	4	13	Twin #2
A	5	0	
A	5	8	
B	5	0	
B	5	14	Low forceps for fetal distress.
B	5	14	Mother severe cardiac.
B	6	1	Twin #1
B	4	3	
C	2	5	Primiparous breech. Died 12 hours.
C	4	8	Primiparous breech. Died 16 hours.
Stillborn	2	2	Premature separation.
Stillborn	Macerated		Dead on admission.

All B infants responded well and required no further treatment other than usual premature care.

TABLE X. SHOWING CLASSIFICATION OF PREMATURE INFANTS

	NO. OF CASES	PERCENTAGE
A (Active)	35	79.6
B (Slightly slow)	5	11.4
C (Slow)	2	4.5
D (Stillborn)	2	4.5
Total	44	100.0

It will be observed that not only were 91.0 per cent of the prematures in satisfactory condition on leaving the delivery room, but also that there is no correlation between the weight of the baby and the degree of respiratory depression. In point of fact is the 1-pound infant who cried vigorously on delivery, only to succumb later to atelectasis. There is little to suggest a respiratory depressant effect in this group.

Cesarean Section Group

To avoid narcotizing the fetus, it has been the practice in this clinic to premedicate patients undergoing cesarean section with atropine only. Such minimal premedication renders the anesthetic induction trying to both patient and anesthetist in the case of general anesthesia, while operating under local anesthesia is usually made no easier by an alert, frequently apprehensive patient. When, during the course of this study, it became apparent that demerol exerted no demonstrable depressant effect on the baby, the use of the drug was extended to include the premedication of cesarean section patients.

TABLE XI. SHOWING CONDITION OF CESAREAN SECTION BABIES

NO. OF CASES	CONDITION	AVERAGE LENGTH OF MEDICATION
14	A	30 minutes
2	B	1 hour, 45 minutes
1	C	45 minutes

Of the two slightly slow babies noted in Table XI, one was obtained at operation in which one hour of operating time was consumed before the infant was delivered. The slow baby was delivered following antepartum hemorrhage from a complete placenta previa.

Since the inception of demerol premedication, those patients receiving general anesthesia have been relatively free from mucus and excitement during the induction. Patients undergoing operation with local anesthesia have had uniformly satisfactory amnesia.

Intravenous Use

That the intravenous use of demerol has no more effect on the fetus than the intramuscular route is shown by Table XII.

TABLE XII. SHOWING FETAL EFFECT OF INTRAVENOUS USE

DOSE	A		B		C		STILLBORN	
	NO.	%	NO.	%	NO.	%	NO.	%
50 IV—50 IM	97	89.8	6	5.6	2	2.8	3	1.8
100 mg. IV	26	89.6	3	10.4	—	—	—	—

In addition, it may be seen that the incidence of active babies is almost identical, whether the patient received 50 or 100 mg. intravenously. Both of the slow babies were discharged as normal with the mother. Of the three stillborns, two were erythroblastotic and dead on admission, while the third was a 2-pound macerated infant.

Delivery Without Anesthesia

In a group of 37 patients who precipitated without anesthesia, any depressant effect of the analgesia would become apparent, there being no masking by an inhalation anesthetic. As will be seen in Table XIII, all of the newborn infants except 2 were active. The one slow baby was a 4-pound premature delivered following ante-partum bleeding from a ruptured marginal sinus in a grade I pre-eclamptic. The stillborn was a 2-pound macerated fetus.

TABLE XIII. CONDITION OF NEWBORN DELIVERED WITHOUT ANESTHESIA

CONDITION	NO. OF CASES
A	35
B	—
C	1
Stillborn	1
Total	37

Summary and Conclusions

Demerol and scopolamine have been used in a series of 1,000 cases for the purpose of studying the maternal and fetal effects of this combination when used as an obstetrical analgesic. Because our primary purpose in medication is establishing complete amnesia, we incorporate scopolamine in our routine as the amnesic drug of choice. Demerol is used to obtain psychic sedation through its analgesic effect, thereby securing a favorable background for the action of scopolamine, reducing the excitement, and enhancing the amnesia.

1. The uncorrected incidence of satisfactory amnesia is 70.5 per cent, where satisfactory amnesia is taken to mean either absolute amnesia, or at the most, the recollection of two or three isolated incidents where no pain is recalled. If this figure is corrected for cases receiving medication either too late, or so infrequently as to nullify the therapeutic effect, the incidence of satisfactory amnesia rises statistically to 90.4 per cent. It is our opinion that while demerol possesses other properties that make it more desirable for purposes of obstetrical analgesia than the barbiturates, it falls slightly short of the barbiturates in providing satisfactory amnesia as measured by our standards.

2. The average primiparous labor in this series was 12.4 hours, the average multiparous labor 7.6 hours. This is a reduction of 2.5 hours in the primiparous labor and 1.2 hours in the multiparous labor when compared with a series of 500 patients in this hospital who received barbiturate analgesia. Since this represents a 17 per cent and 14 per cent reduction respectively, we believe it to be significant.

3. As a preanesthetic medication, demerol is not surpassed by the other preanesthetic combinations in common use. The amount of anesthetic agent required is approximately the same as in those patients receiving barbiturates. There were no major pulmonary complications.

4. Intravenous administration has been employed in those patients admitted in active labor and expected to deliver within 2 hours. It has also been used for premedicating cesarean sections. The incidence of satisfactory amnesia is approximately the same as in those patients receiving intramuscular medication, despite the fact that 63 per cent of the patients were medicated for less than one hour. No increased hazard has been demonstrated in association with the intravenous route.

5. The only maternal untoward effects in the series were seen in the intravenous group. With the exception of transient nausea in one-fourth of the cases, no further side effects were seen when the drug was administered slowly, taking a minimal two minutes by the clock to inject 2 c.c. (100 mg.).

6. The analgesic properties of demerol are demonstrated by a series of 37 patients delivered without anesthesia, of whom 79 per cent could recall no pain whatsoever.

7. Demerol exerts no demonstrable depressant effect on either full-term or premature infants, whether administered by the intramuscular or the intravenous route.

In view of the satisfactory amnesia, the absence of pulmonary complications, and the freedom from depressant effect on the fetus, it is our opinion that demerol in conjunction with scopolamine is superior as an obstetrical analgesic to other analgesics in common use.

We wish to thank Dr. Bert Hershenson for his assistance in obtaining the data on preanesthetic effect, and Dr. Monrad E. Aaberg for his assistance in interviewing patients.

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CONTINUOUS CAUDAL ANESTHESIA IN 200 OBSTETRIC PATIENTS

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THE publication of an article in 1942 by Edwards and Hingson[1] on the use of continuous caudal anesthesia created a widespread interest in the subject and since that time numerous reports have been published.[2-12] This article is an analysis of our experience with this method.

Material

Our study is based on a series of 200 consecutive obstetric patients in whom continuous caudal anesthesia was employed routinely in order to determine its practicability.

In 5 instances, the anesthesia was unsatisfactory and inhalation anesthesia was used in the second stage. In 195, or 97.5 per cent of our cases, the method was successful. The period of anesthesia varied from 30 minutes to 24 hours 30 minutes, with an average of 4 hours 20 minutes for primiparas and 2 hours 45 minutes for multiparas. The average duration of the first stage in the primiparous group was 9 hours 4 minutes and the second stage 34 minutes; while for the multiparas it was 8 hours 12 minutes and 32 minutes respectively.

One hundred-three (103) patients were primiparas and 97 multiparas. A vertex presentation was found in 195 instances, of which 30 were persistent occiput posterior or transverse. There were 2 face* and 3 breech presentations. A spontaneous termination of labor occurred in 62, or 63.9 per cent of the multiparas, but an operative delivery was necessary in all the primiparas. An episiotomy was employed in 156, and minor lacerations of the perineum occurred in only 8 instances.

Two patients had a pre-eclamptic toxemia. In 2 cases of placenta previa the patients were successfully delivered with the use of hydrostatic bags. Four cases of uterine inertia were encountered, but the careful employment of pitocin in small doses resulted in delivery without difficulty. In 4 patients a test of labor was conducted because of cephalopelvic disproportion, and 2 of these were finally subjected to cesarean section. In one case, the operation was carried out by increasing the dosage of the drug in order to obtain a higher level of abdominal skin anesthesia, and in the other, by changing to an inhalation anesthetic.

Contraindications

Several important contraindications to the use of caudal anesthesia have been emphasized by various authors. The first was directed to difficulties inherent with the introduction of the needle because of abnormalities of the sacrum, such as variations in the curvature of the sacrum, spina bifida, or failure of fusion of one or more of the poste-

*An increasing number of face presentations has occurred while using caudal anesthesia with the patients in the modified Sims' position.

rior arches. In a survey of 100 x-ray photographs, we noted that variations in the classical descriptions of the pelvis occurred in four out of five sacra, but probably not one in 100 is extensive enough to preclude the use of continuous caudal anesthesia.

The presence of infective processes about the sacral area is of prime importance. For example, one patient was not given this type of anesthetic because of a generalized folliculitis. The possibility of introducing an infection into the sacral canal must be remembered always as a possible serious complication.

A hypersensitivity to local anesthetic agents also must be kept in mind, but in this series a history of previous manifestations of this type was not obtained.

In some instances, mental or psychic aberrations make it impossible to trust the patient to follow the necessary simple instructions. This was observed in one case and it became necessary to remove the needle after the caudal anesthesia had been started.

Technique

A distinct advantage in this study was the fact that caudal anesthesia had been employed on our service during the second and third stages of labor in over 500 deliveries previous to the adoption of the continuous method, and we feel that a thorough fundamental training of the operator is necessary for its success.

Stage of Labor When Anesthetic Is Begun.—In general, the statement of Edwards and Hingson, that "continuous caudal anesthesia is started when the patient is in labor and in distress," has been our basis for determining when to start the procedure. As a rule, this was found to be when the cervix was dilated 3 cm. and the contractions occurred every five minutes or less and lasted for 20 seconds or more.

Premedication.—It is accepted that premedication with barbiturates decreases the toxicity of local anesthetics from 3 to 5 times. For this reason nembutal, seconal, or a combination of sodium amytal and seconal in 3-grain doses was given 15 minutes prior to beginning the anesthesia. Seven patients failed to receive premedication, and one had a moderately severe toxic reaction with hallucinations and clonic muscular contractions. This condition lasted for 90 seconds but did not necessitate abandonment of the anesthetic.

Drug and Dosage.—Metycaine was used in all instances. It was prepared by dissolving the powder in normal saline as a 1.4 per cent solution. The initial dose varied from 30 to 45 c.c., with subsequent injections of 20 c.c. at intervals of from 30 to 90 minutes, with an average of 50 minutes. The total amounts employed varied from 45 to 330 c.c., the average for primiparas being 110 c.c. and for multiparas 65 c.c. As a safety measure, the level of cutaneous anesthesia must be constantly supervised, and should not rise above the umbilicus, as recently emphasized by Block and Rotstein.[9]

Insertion of Needle.—The equipment employed in this series was similar to that described by Edwards and Hingson. In our first 90 cases, the patient was placed in the knee-chest position during the in-

sertion of the caudal needle. After injection and attachment of the tubing, the patient was placed on her back with a pad over the needle, a small pillow beneath the knees, and a pad under the lumbar spine. This assisted in straightening the exaggerated lumbar lordosis as the muscle tension relaxed with the anesthesia and resulted in a reduction of post-partum backache. This technique, however, was discontinued since severe bending of the needle would occur at two places; one at the junction of the needle and the sacrococcygeal ligament and the other at the junction of the needle and the skin (Fig. 1). It was demonstrated that motion of the soft parts and fascia over the sacrum during the change from knee-chest to dorsal recumbent position caused this distortion of the needle and occasionally resulted in a withdrawal of the point to a level in the caudal canal where further injections were ineffective, thus making reinsertion of the needle necessary.

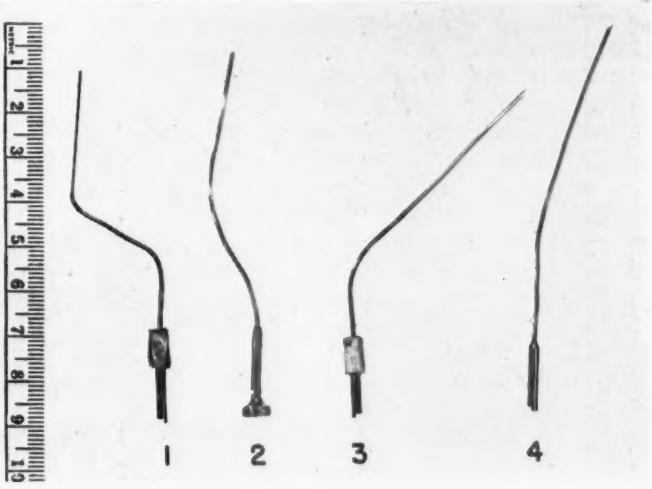

Fig. 1.—Photograph of needles obtained after injection into the sacral canal to induce caudal anesthesia. Numbers 1 and 2 show the bending which occurred when the patient was in the knee-chest position during insertion of the needle. Numbers 3 and 4 were obtained from patients who were lying prone when needle was inserted into the sacral canal.

Our present method is to place the patient in the prone position with a pillow under the thighs. The sacral hiatus is palpated, a skin wheal raised with metycaine solution, the sacrococcygeal ligament infiltrated, and the malleable stainless steel needle inserted. The needle is held in place with ¼-inch strips of adhesive tape extending from the left iliac crest down to and around the hub of the needle and up to the right iliac crest to form a "V." A split alcohol sponge is placed around the needle and the patient carefully turned to a modified Sims' position, where she remains. She is aided in changing from one side to the other with each subsequent injection. It is important to remember that 90 per cent of these patients are completely helpless as far as motor power in the lower extremities is concerned. This latter technique has been extremely satisfactory, causing little or no distortion and no breaking of the needle.

Management Prior to Moving Patient to Delivery Room.—When the cervix is completely dilated and the head is on the perineum, or when, in the judgment of the obstetrician in charge, the patient can be de-

livered within one hour without unwarranted interference, the caudal needle is removed and the patient then taken to the delivery room. In most instances, if injection has not been made during the preceding 20 minutes, 20 c.c. of metycaine are given before withdrawal of the needle. This technique is employed in primiparas and multiparas alike, and we should like to stress the point that moving the patient without first removing the caudal needle constitutes an unnecessary risk.

Complications

A number of hazards are associated with this type of anesthesia and various precautions to prevent complications cannot be too strongly emphasized.

Intravenous Injection of Anesthetic Agent.—This may be prevented by careful aspiration before the metycaine is injected and by taking pains to turn the needle so that it does not ride along the anterior or posterior wall of the sacrum during insertion. In two instances in our series blood was aspirated after 5 to 10 c.c. of metycaine solution had been injected. Both patients suffered toxic reactions lasting 30 to 40 seconds, with clonic contractions of the muscles of the limbs and neck. Recovery, however, was rapid; the position of the needle was changed and the caudal anesthesia continued successfully.

Breaking of the Needle.—In four cases we experienced this complication and feel that the important responsible factors were: (1) employment of the knee-chest position for the preliminary injection; (2) allowing the patient to remain on her back; (3) moving her from the first-stage room to the delivery room without *first* removing the caudal needle; (4) repeated use of the same needle; and (5) the selection of German silver needles.

The use of the prone or lateral position during insertion of the needle, the employment of specially designed stainless steel malleable needles (Becton-Dickinson and Company), limiting the use of each needle to three times or less, and removing the needle before transporting the patient to the delivery room have eliminated this hazard almost completely.

Infection.—The prevention of infection at the site of injection requires extreme care in aseptic technique. The area selected must be prepared with suitable antiseptic agents and draped with sterile towels. The operator must wear sterile gloves, insert the needle, make the initial injection of 30 to 40 c.c. of metycaine and attach the tube from the metycaine bottle, tape the needle in place and then place a sterile split alcohol square about the hub of the needle. When the needle is removed, a sterile dressing must be placed over the puncture wound. One local infection occurred in our series, following surgical removal of a broken needle.

Marked Fall in Blood Pressure.—An alarming fall in blood pressure occurred in 5 cases. We believe this was due to marked vasodilatation in the anesthetized areas in patients with vasomotor instability. In these cases the blood pressure dropped to 70 mm. of mercury systolic or less; there was a remarkable decrease in pulse pressure, the pulse rate increased slightly, and the patients were pale and dry. This, however, is not an immediate complication, and the patients responded uniformly well to 3 or 4 minimums of neosynephrine given intramus-

cularly. In no instance did it necessitate discontinuing the anesthetic and no subsequent ill effects were noted in either mother or child.

Toxic Symptoms.—We observed that the speed of injection and the volume of the solution employed during the initial injection were important factors in the production of immediate toxic symptoms. Nausea and vomiting within 60 seconds of injection were encountered in 7 per cent of our cases. Some of these patients experienced brief bouts of nausea with each subsequent injection. It is the opinion of some authors that this manifestation, difficult as it may be to evaluate during pregnancy, occurs with no greater frequency in patients subjected to caudal anesthesia than in patients carried through labor by other methods. However, we failed to find a single patient who was willing to have the anesthetic discontinued because of this symptom.

Headaches and dizziness were occasional complaints. Syncope-like attacks were noted in two cases, and both were associated with definite evidence of intravenous injection of small amounts of the drug. One patient in the group not receiving premedication showed a very definite toxic reaction, as mentioned before, but it was not necessary to discontinue the anesthetic.

Injection of Solution Into Subarachnoid Space.—In more than 700 caudal injections, this accident, which may be serious by producing massive spinal anesthesia, was not encountered by us. Its prevention lies in careful aspiration before introducing the solution.

Injury to Sacral Region.—This complication was not experienced in this group, but it nevertheless is a potential hazard. An attempt was made to use ureteral catheters, as recommended by Adams et al,[6] but we felt that the employment of larger needles increased the possibility of injury to the sacrum.

Increase In Operative Deliveries.—A large percentage of our series was delivered by operation, chiefly low forceps in vertex presentations. The explanation lies in the fact that with the absence of pain, it is difficult to obtain the cooperation of the patient in expelling the baby during the second stage. It should be noted, however, that in occiput posterior or transverse presentations, rotation with forceps was facilitated by caudal anesthesia, due to the complete relaxation of the perineum and pelvic musculature.

Post-partum Complications.—Post-partum conditions directly accreditable to the caudal route of anesthesia were low back pain and increased irritability of the patients. In our experience, the low back pain occurred as soon as the anesthesia wore off. It lasted for 2 to 6 hours, and was present in about 12 per cent of our patients. This condition can be easily controlled with analgesic drugs and does not constitute a serious drawback to this method.

The increased irritability occurred most frequently in primiparas. It was not of serious consequence, usually consisting of bitter complaints about routine post-partum care and disappearing after 24 hours.

Conclusions

1. Continuous caudal anesthesia was employed in 200 consecutive obstetric patients, in whom satisfactory results were obtained in 195 instances.

2. No obstetric complications which could be considered as contraindicating the usage of this procedure were encountered by us.

3. The most important complications to look out for are the intravenous or subarachnoid injection of the drug, infection, breaking of the needle, fall in blood pressure, toxic manifestations, and trauma to the sacrum.

4. An increase in the number of operative deliveries was observed.

Our thanks are due to Eli Lilly and Company for a donation of metycaine, sodium amytal and seconal used in this study.

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FINDINGS IN ROUTINE PELVIC EXAMINATIONS ON 1,998 WOMEN*

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A SURVEY of the literature reveals a remarkable poverty of statistical information on the pelvic findings in groups of presumably healthy women. Most textbooks give the incidence of these findings only on the basis of general impressions and in the most general terms. The few available statistical studies in the literature of the past twenty years[1-5] for the most part deal with pelvic findings in hospital admissions, psychotic patients, and parous women. Only one study similar to the one being presented was found; that of Dunn in which 572 pelvic studies were done in the course of general physical examinations on supposedly healthy women from 20 to 65 years of age.[6] However, this group includes a much higher percentage of parous women if one may judge from the high incidence of cervical lacerations. The above study is, therefore, not strictly comparable to the one reported here.

The opportunity for this study was afforded by the active duty physical examinations, which were given all the apprentice seamen (WR) entering the Naval Reserve Midshipmen's School (WR) at Northampton, Massachusetts.

The physical examinations were given as soon as the women reported for active duty. Four classes are reported in this study, totaling 1,998 in all. Approximately 15 were examined per hour. The physical examination includes general body and neuropsychiatric examination, eye, ear, nose and throat examination, examination of heart and lungs, including pulse and blood pressure response to exercise, abdominal and vaginal or rectal examination, blood Kahn test and blood typing, followed by dental charting and photofluoroscopic examination of the chest. Each part of the physical examination is performed by a medical officer specializing in the particular branch of medicine involved. The pelvic and abdominal examinations reported here were all done by the authors. Pelvic examinations, either rectal or vaginal, are done with the patient in the usual lithotomy position. These are done irrespective of the menses. The abdomen is first palpated and the external genitalia are inspected. The state of the introitus determines whether vaginal or rectal examination is used. Rectal examination was necessary in 132

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cases, or 6.6 per cent of the total cases. In 888 of the candidates a two-finger vaginal examination could be performed. Corresponding sizes of specula were used. Cervical cultures were taken on the first 1,468 women; on the last 530, they were taken only when indicated. These cultures are grown on proteose No. 3 and bactohemoglobin media, in Novy jars containing about 10 per cent carbon dioxide.

The composition of the group is shown by the following Table:

MARITAL STATUS	21 TO 25 YR.	26 TO 30 YR.	31 TO 40 YR.	41 TO 50 YR.	TOTAL
Total Exam.	944	583	422	49	1,998
Widow	4	3	5	3	15
Separated	1	1	1	0	3
Divorced	2	9	21	5	37
Married	30	30	49	13	122
Single	907	540	346	28	1,821

There are many factors which made this group a highly selected one. As can be seen from the above Table, there is a selection as to age and 91 per cent are single. Only 27 gave a history of any pregnancies.

All the women examined had a minimum of two years' college education; the great majority possessed at least a Bachelor's degree. The biggest factor of selection, however, is that all these women had a previous physical examination at their Navy Procurement Offices. In most cases, because of lack of facilities, these examinations did not include pelvic or rectal examinations. In the last group of cases examined in February, 1943, only 35.8 per cent had a previous pelvic examination. We know that prior to this time, very few Procurement Offices did pelvic examinations. It is estimated that only 5 per cent to 15 per cent of the previous groups were given this part of the examination before reporting for active duty.

About one-third of the girls examined at one of the large Procurement Offices failed to meet physical standards. We have no statistics available on the number disqualified for pelvic defects at that Naval activity.

The following are considered definitely disqualifying gynecologic defects according to the directive issued by the Bureau of Medicine and Surgery:

1. History of abnormality of the menstrual cycle, particularly disabling dysmenorrhea and amenorrhea unless determined to be the result of natural or artificial menopause.
2. History of chronic pelvic inflammation or an acute infectious pelvic disease.
3. Finding of congenital anomalies of clinical significance.
4. Conditions of pelvic organs which are considered likely to interfere with the performance of duty or to require surgical intervention.
5. Cervical culture found repeatedly positive for gonococci.

At the time of the physical examination the medical history is obtained. A detailed consideration of dysmenorrhea, amenorrhea and other abnormalities of the menstrual cycle would be valueless, because of the elimination of any candidate with any of these conditions by the Procurement Medical Officers. Also, the women are reluctant to admit readily the existence of disabling dysmenorrhea since they know it is disqualifying.

The following summary of gynecologic and obstetric histories as obtained by us is considered on the whole reliable:

Appendectomy	301
Supracervical hysterectomy	13
Myomectomy	1
Salpingectomy, bilateral	1
Salpingo-oophorectomy, unilateral	4
Oophorectomy, unilateral	10
bilateral	1
Cystectomy, ovarian	14
Resection of ovary	4
Dilatation and curettage	17
Suspension of uterus	12
Radium insertion for hemorrhage	1
Adhesions, lysis of	2
Sympathectomy, presacral	1
Polypectomy, cervical	1
Inguinal hernia repair	1
Meckel's diverticulum	1
Exploratory laparotomy	2
Vaginal cyst removed	1
Excision, Bartholin's cyst	1
Menopause	3
Metrorrhagia	2
Pregnancies	
Full-term delivery	8
Stillbirth	1
Premature stillbirth	1
Miscarriage— 3 months	11
3½ months	1
6 months	2
Ectopic pregnancies	3

For purpose of study, we have divided the women into age groups of 20 to 25, 26 to 30, 31 to 40, 41 to 50 years. There were 1,279 women with normal pelvic findings. The defects listed below were found in the remaining 719.

DEFECT	20 TO 25		26 TO 30		31 TO 40		41 TO 50		TOTAL	
	No.	Per 1,000	No.	Per 1,000	No.	Per 1,000	No.	Per 1,000	No.	Per 1,000
TOTAL CASES	945		583		421		49		1,998	
Pregnancy	3	3.2	0	0.0	1	2.4	0	0.0	4	2.0
Perineal lacerations	0	0.0	1	1.7	3	7.1	1	20.4	5	2.5
Bartholin cysts	0	0.0	1	1.7	1	2.4	0	0.0	2	1.0
Rectocele	0	0.0	0	0.0	0	0.0	1	20.4	1	0.5
Partial septum of vagina	1	1.1	1	1.7	0	0.0	0	0.0	2	1.0
Vaginitis—senile	0	0.0	0	0.0	1	2.4	3	61.2	4	2.0
Vulvovaginitis undifferentiated	5	5.3	10	17.2	6	14.3	2	40.8	23	11.5

DEFECT	20 TO 25		26 TO 30		31 TO 40		41 TO 50		TOTAL	
	No.	Per 1,000	No.	Per 1,000	No.	Per 1,000	No.	Per 1,000	No.	Per 1,000
Cervix erosion										
Slight	68	72.0	39	66.9	16	38.0	3	61.2	126	63.1
Moderate	17	18.0	19	32.6	16	38.0	1	20.4	53	26.5
Cervicitis										
Moderate	9	9.5	8	13.7	3	7.1	1	20.4	21	10.5
Marked	1	1.1	1	1.7	0	0.0	0	0.0	2	1.0
Cystic	7	7.4	9	15.4	13	30.9	1	20.4	30	15.0
Endocervicitis	5	5.3	1	1.7	6	14.3	0	0.0	12	6.0
Total cervical erosions and cervicitis	107	113.2	77	132.1	54	128.3	6	122.4	244	122.1
Healed lacerations	2	2.1	3	5.1	6	14.3	3	61.2	14	7.0
Polyps	0	0.0	1	1.7	5	11.9	2	40.8	8	4.0
Cervical cultures positive for gonorrhea	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Uterus										
Infantile	8	8.5	4	6.9	1	2.4	0	0.0	13	6.5
Bicornuate	0	0.0	0	0.0	2	4.8	0	0.0	2	1.0
Enlarged, firm	3	3.2	3	5.1	11	26.1	1	20.4	18	9.0
Fibromyomas										
Intramural	0	0.0	5	8.6	12	28.5	10	204.1	27	13.5
Subserous	0	0.0	2	3.4	6	14.3	2	40.8	10	5.0
Total fibromyomas	0	0.0	7	12.0	18	42.8	12	244.9	37	18.5
Total fibromyomas plus enlarged, firm uteri	3	3.2	10	17.2	29	67.9	13	265.3	55	27.5
Retrocessed	12	12.7	11	18.9	7	16.6	0	0.0	30	15.0
Retropositions										
1st degree	40	42.3	21	36.0	20	47.5	2	40.8	83	41.5
2nd degree	42	44.4	39	66.9	23	54.6	5	102.0	99	49.5
3rd degree	16	16.9	16	27.4	16	38.0	1	20.4	49	24.5
Lateral displacement										
Right	4	4.2	1	1.7	3	7.1	1	20.4	9	4.5
Left	6	6.3	2	3.4	1	2.4	0	0.0	9	4.5
Prolapsus, 1st degree	1	1.1	1	1.7	3	7.1	1	20.4	6	3.0
Total malpositions	119	125.9	90	154.4	73	173.2	10	204.1	282	141.1
Adnexae										
Ovarian cysts	3	3.2	3	5.1	3	7.1	0	0.0	9	4.5
Cystic ovaries										
Right	7	7.4	7	12.0	2	4.8	0	0.0	16	8.0
Left	18	19.1	4	6.9	4	9.5	0	0.0	26	13.0
Bilateral prolapsed cystic ovaries	5	5.3	0	0.0	1	2.4	0	0.0	6	3.0
Total cystic ovaries	30	31.8	11	18.9	7	16.6	0	0.0	48	24.0
Induration of adnexa										
Right	2	2.1	2	3.4	1	2.4	1	20.4	6	3.0
Left	5	5.3	3	5.1	1	2.4	0	0.0	9	4.5
Bilateral	1	1.1	0	0.0	0	0.0	1	20.4	2	1.0
Total induration of adnexa	8	8.5	5	8.6	2	4.8	2	40.8	17	8.5
Pediculi pubis	1	1.1	0	0.0	0	0.0	0	0.0	1	0.5
Furuncle of perineum	0	0.0	1	1.7	0	0.0	0	0.0	1	0.5
Skenitis culture negative for gonococcus	0	0.0	0	0.0	0	0.0	1	20.4	1	0.5
Congenital opening of urethra on labia minora	0	0.0	1	1.7	0	0.0	0	0.0	1	0.5

Of the preceding findings, the following were disqualifying:

Pregnancies	4
Large bilateral cystic ovaries	1
Ovarian cysts	6
Metrorrhagia	2
Fibromyomas	4

Discussion

The classification used is, of course, a purely clinical one. There was no opportunity to investigate the etiology of minor defects. Some of the terms employed may require some explanation which will be given in the course of the discussion.

Because of the lack of laboratory facilities, no bacteriological investigation of the cases of vaginitis could be made; therefore, only two classifications were made, namely, senile vaginitis and undifferentiated vulvovaginitis.

In the classification of cervical pathology, standard clinical terminology was used. Since the classification is made on clinical impressions, the clinical entities overlap each other. Therefore, the most significant opinion as to incidence should be based on the total cervical erosions and cervicitis. No cervical biopsies were taken. However, no cervical pathology suggestive of carcinoma was found. Here again, one should realize that we are dealing with nulliparous women predominantly.

One of the two bicornuate uteri was previously diagnosed by x-ray. The other is a clinical diagnosis but nevertheless definitely confirmed. The two cases of bicornuate uteri plus the two cases of septate vagina and congenital opening of urethra make a total of five cases of congenital anomalies, or an incidence of 2.5 per 1,000. The term "enlarged, firm uterus" is a purely descriptive one. We found a number of uteri that varied from one and a half to two times the normal size. This entity was more common in those of the fourth and fifth decades. Since the incidence follows that of fibromyomas, the authors are of the opinion that this clinical entity is related to fibromyomas or fibrosis uteri. For this reason, we have added them to our incidence of fibromyomas. The authors realize that the terms "intramural" and "subserous" are not pathologically accurate and represent only the predominant clinical findings in cases of multiple fibromyomas. The fibromyomas varied in size from those two centimeters in diameter to one which extended almost to the umbilicus. Only four of the 37 fibromyomas were of sufficient size or clinical significance to require surgical intervention. These women were disqualified. Fourteen women gave a history of hysterectomy or myomectomy for fibromyomas. This number added to the 55 found in this study gives an incidence of 34.5 cases per thousand examined in this group.

The classification of retroposition was used instead of dividing the cases into retroflexions and retroversions. The authors felt that the difference would be too easily missed in the course of the quick pelvic

examination and, therefore, the term "retroposition" would be more accurate. Twelve women stated that they had had suspensions of the uterus. Ten of these stated that dysmenorrhea was the indication for this operation.

The association of erosion or cervicitis and retroposition is often mentioned. Thirteen and nine-tenths per cent of the 267 women having retroversion, retroflexion or retrocession of the uterus had some degree of cervicitis or erosion. However, an incidence of 13.8 was found in the total group in which the cervix was visualized. There is, therefore, no correlation between cervical erosion or cervicitis and retroposition.

Eighteen cases of lateral displacement were found in the entire group. No cause for this displacement could be discovered in eleven of these cases. In two cases cystic ovaries had pulled the uterus laterally; ovarian cysts accounted for two of the cases; and induration of the adnexa for three others.

The ovarian cysts varied in size from one small one, 3 centimeters in diameter, to one 10 centimeters in diameter. Six of the nine cases of ovarian cysts were large enough to be considered operable and, therefore, disqualifying. Sixteen women gave a history of having had one or both ovaries removed. Therefore, 22 women, 11.0 per thousand of the 1,998 examined, had had surgery or required surgery for ovarian pathology at the time of the examination. One of the patients having cystic ovaries was disqualified because both were over three times the normal size. They were prolapsed and exquisitely tender.

Of the sixteen cases of induration of the adnexa, five gave no history of previous pelvic disease or operation. Twelve had had operative procedures which would account for the induration. Two of these operations were performed because of pelvic inflammatory disease.

Because of the small number of married or parous women, no correlation of pathology with these factors was attempted. The numbers in the higher age groups were small, but the authors considered them adequate to give a rough correlation of pathology with age. The correlation of healed perineal and cervical lacerations is an obvious one. Similarly, there is a definite increase in the incidence of senile vaginitis. However, undifferentiated vulvovaginitis also increased with age. Cervicitis had, however, no significant incidence variation per decade of life. The number of cervical polyps discovered was small, but here again there is a definite increase in the older age groups. The sharp correlation of the incidence of fibromyomas with age is the expected one. First-degree prolapsus uteri and total malpositions also increase with the age.

Summary

Routine pelvic examinations were done on a group of 1,998 presumably healthy, white women in the younger age levels. Approxi-

mately one-third of the women had some type of gynecologic condition predominantly of minor nature. The incidence of major pathology as presented here errs on the side of conservatism since some 10 per cent to 15 per cent of the women had previous pelvic examinations at the Procurement Offices, and some cases were undoubtedly eliminated because of major pelvic pathology. Despite this, the figures on incidence of fibromyomas uteri and ovarian cysts are higher, in the authors' opinion, than would be expected. The total incidence of fibromyomas was 27.5 per thousand, which is higher than one would expect in a predominantly young group. Nine ovarian cysts were found, six of which were large enough to require operation.

Naturally the incidence of minor pathology would not be affected by any elimination due to previous pelvic examinations. The incidence of vaginitis per thousand was 13.5; total cervical erosions and cervicitis 122.1; cervical polyps 4.0; total malpositions 141.1; total cystic ovaries 24.0; and induration of the adnexa 8.5. These figures should represent the incidence per thousand in any similar group.

Of the 1,998 women examined, ten were candidates for major surgery. Two cases, because of a history of metrorrhagia, were rejected and presumably would undergo diagnostic curettage. Eight cases required removal of cervical polyps. Twenty-seven had vaginitis. Two hundred and forty-four had cervical erosions or cervicitis. According to current gynecologic practice, treatment is advisable in these cases. This large group requiring treatment (291 out of 1,998) once again emphasizes the need for careful routine pelvic examinations.

Conclusions

1. There is an obvious need for routine pelvic examinations not only in women of the menopausal age but also in younger women.

2. Vaginal examinations are possible regardless of marital status in all but a very small minority.

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A COMBINED EXTRAUTERINE AND INTRAUTERINE PREGNANCY

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COMBINED extrauterine and intrauterine pregnancy, although infrequent, is by no means rare as once was thought. These cases are always of interest because of their diagnostic difficulties and resulting high mortality rate. Gemmell and Murray[2] in their analysis of 217 cases, computed a mortality rate of 20.7 per cent for the entire series, or 14.4 per cent if those cases were excluded which were diagnosed only at autopsy without any previous treatment. It is the purpose of this report to point out that since this condition is occasionally encountered and since the mortality rate is high, the possibility of a combined pregnancy should be kept in mind in a differential diagnosis.

The extrauterine rather than the intrauterine pregnancy is the dangerous factor. Frequently, the diagnosis of extrauterine pregnancy is made, but the patient will abort (as in the case to be reported) via vagina, and one is misled into the false diagnosis of incomplete or completed abortion with infection or uterine injury. In other cases, the diagnosis of extrauterine pregnancy is made with some reservation and upon doing a diagnostic curettage and recovering placental tissue, the extrauterine pregnancy is overlooked until later, sometimes too late.

In computing the number of cases to date, the literature is confusing, overlapping and incomplete. Duverney,[1] in 1708, is given credit for reporting the first case, found in a post-mortem examination. However, without much doubt, combined pregnancies must have occurred prior to this date. In spite of the supposedly careful compilations by other reviewers, cases have been omitted by them. There must be many unreported cases and many journals unavailable to most authors, so that an accurate collection of cases is impossible. Mitra[11] and Ludwig[8] both reviewed the recent literature in 1940, yet in only a few instances did their cases overlap.

Novak[1] in 1926 made an exhaustive study from 1708 to 1926 quoting Duverney, Zinke, Simpson and Neugebauer. He differentiated between compound and combined intrauterine and extrauterine pregnancies. The former was believed to be more frequent and referred to an extrauterine pregnancy with spontaneous resolution or lithopedion formation and subsequent intrauterine pregnancy. The latter he considered rarer and referred to both pregnancies occurring at the same time. His total of cases, including 32 from recent literature and two of his own, up to 1926, was 276. Gemmell and Murray[2] made "a limited survey of the literature" and reported 217 cases up to 1931, including two cases of their own and two cases reported in 1932. They gave recognition to Novak's article[1] and the cited 276 cases. They believed some of the cases were not combined, but twin pregnancies in the tubes or in two horns of bicornuate uteri. They themselves reported only those cases in which they personally studied the original article or an abstract of it. Mathieu[3] reviewed the literature through 1936 and added 57 cases which had not been reported by Gemmell

and Murray or Novak, thus making the total either 274 (if added to Gemmell's figure) or 333 (if added to Novak's). Sloat and Peterson[4] tabulated the cases added by Novak, Stein and Gemmell, and found that there were 64 new cases which could be added to Neugebauer's 244 cases cited in 1913. They added 15 cases from the literature which had not appeared in previous tabulations in addition to one case of their own, bringing a revised total of 324 up until 1936. However, in December, 1939, Rosenthal[7] went back to Heffernan's review in 1935, of 277 cases and added 9 cases which he found since in the literature (without enumerating them) plus one personal case, totaling 287 cases. Ludwig[8] reviewed 17 cases in the literature since Mathieu,[3] plus 3 cases of his own and adding them to Mathieu's brought the total through 1938, to 294 (using Gemmell's figures) or 353 (using Novak's). Mitra[11] also reviewed the literature from Duverney and stated that up to 1940, there were only 304 cases cited, including two of his own. The recent literature has been reviewed for this report, and 15 cases not included by Ludwig, and 18 not included by Mitra have been discovered.[4-17] This brings the total to either 322 (by adding to the compilation of Mitra) or 309 to 368 (by adding to the estimate of Ludwig).

The case to be reported is interesting because of the possibilities the patient presented in a different diagnosis. It is the first instance of this condition encountered in Bellevue Hospital since 1918.

R. M. (38747-43), a 28-year-old, married, colored female, gravida ii, para ii, was admitted to the gynecological service at 11:00 P.M. on 8/17/43. Her chief complaint was abdominal pain. Her menstrual periods had always been regular, her last menses having occurred 6/17/43. She had missed her July period, but had no subjective signs or symptoms of pregnancy. Approximately two weeks before her admission to the hospital, she began to pass small blood clots *per vaginam* with gradual increase in bleeding and then subsidence, so that on admission she had merely pinkish spotting. About four days before her admission, following an indefinite period of generalized abdominal tenderness, the patient developed sharp intermittent pains in both lower quadrants. On admission, pain was localized to the right lower quadrant with transmission to the rectum. She suffered from nausea, but had not vomited. The history of the background of the patient supplied two pertinent facts: (1) Both the patient's mother and mother-in-law had twin pregnancies. (2) In 1941, patient was treated for "inflammation" in her pelvis by bed rest for one month.

Physical Examination.—Blood pressure 120/80, pulse 90, respirations 20, temperature 99° F. Patient was a moderately obese, colored female of stated age, who appeared uncomfortable, but not in acute distress. General physical examination was essentially negative. Breasts showed Montgomery's tubercles to be present, but no secretion could be demonstrated. The abdomen was full and soft with some resistance to light palpation in the right lower quadrant. There was tenderness to deep palpation over entire abdomen with rebound tenderness, being most marked in the right lower quadrant. The abdomen was tympanitic throughout. Pelvic examination revealed a relaxed two fingers' introitus. The cervix was irregular, soft, tender on motion, pointing in the axis of the vagina, and the external os admitting a finger tip. The uterus was enlarged to about the size of a 3 months' pregnancy, fixed, very tender and in midposition. The adnexa showed marked tenderness, and on the left side, a flattened 4 by 8 cm., firm, thickened mass which ex-

tended into the cul-de-sac. Speculum examination revealed a positive Chadwick sign, old lateral laceration of the cervix with ectropion and a light-brown dirty discharge. Rectovaginal examination confirmed the above findings.

Laboratory Data:

W.B.C.	10,400
R.B.C.	4,800,000
Hgb.	14 Gm.
Sedimentation rate	25 min. (18 mm.)
Urinalysis, Specific gravity 1.033, Alkaline reaction, no albumin, 1+ sugar and rare W.B.C. per high power field.	

A tentative diagnosis of left tubal pregnancy with tubal abortion was made. However, because of the large size of the uterus, rapid sedimentation rate and history of pelvic inflammation, the possibility of intrauterine pregnancy with bilateral chronic adnexal disease was considered. She was seen 12 hours later by an attending physician who made the diagnosis of threatened uterine abortion and advised expectant treatment.

On August 22, 1943, at 6:45 P.M. (5 days after her admission) patient spontaneously aborted a fetus about 8 weeks in size, together with placental tissue. Patient's temperature rose to 103° F., and remained elevated for the next six days. Lower abdominal pain became increasingly severe. During this time, five pelvic examinations were made by various attending physicians. The following diagnoses were considered: Fibromyomata uteri, tuboovarian abscess, infected ovarian cyst, acute degeneration of a fibroid.

On 9/1/43, the mass which had been felt previously in the cul-de-sac was found on examination to have disappeared and an immediate laparotomy was advised. Laparotomy revealed a ruptured left tubal pregnancy. A left salpingectomy was performed. Since the accumulated blood in the cul-de-sac had a definite colon odor, the abdomen was drained. Except for considerable discharge from the lower angle of the wound, she had an uneventful recovery.

Pathological Report:

(a) Material expelled from the uterus (Accession No. 2393-1943). Degenerating decidua and placental tissue.

(b) Mass removed at laparotomy (Accession No. 2240-1943).

Left tubal pregnancy with external rupture.

Chronic follicular salpingitis.

In both specimens, the placental tissue showed relatively little degeneration and appeared quite similar, showing without doubt, that the pregnancies were simultaneous or combined rather than sequential or compound.

Comment

Combined extrauterine and intrauterine pregnancies are not as rare as is commonly believed. A review of the literature up until 1942 reveals the number of such cases reported to total between 309 and 368, the actual number probably being much greater. Since this unusual form of binovular twin pregnancy is not rare, it should be borne in mind whenever a patient who appears to have an intrauterine pregnancy suffers from unusual pain and bleeding during the early months of

gestation. The possibility of an associated tubal pregnancy is greatly increased if a tender adnexal mass can also be made out. A family history disclosing a predisposition to multiple pregnancy or a previous history of adnexal disease may be of some value.

A review of the literature shows that the most favorable outcome results when the ectopic pregnancy undergoes rupture without disturbing the uterine gestation. In such cases, the ectopic pregnancy manifests itself first, is recognized and promptly brought to surgery. In an analysis by Morse[6] 40 per cent of combined pregnancies followed such a course, and the intrauterine pregnancy proceeded normally to term.

Gemmell and Murray[2] subdivided their cases into definite groups and computed the mortality rate in each such group. Their results were as follows:

1. Cases discovered at autopsy.	16 cases	16 deaths	100%
2. Cases discovered after delivery of uterine pregnancy.	41 cases	6 deaths	14.6%
3. Cases discovered during the second half of pregnancy or during labor.	20 cases	7 deaths	35%
4. Cases discovered during the first half of pregnancy after abortion of the uterine pregnancy.	47 cases	7 deaths	15%
5. Cases discovered during the first half of pregnancy before abortion of the uterine pregnancy.	93 cases	9 deaths	9.7%

From this study, it appears the group of cases which has yielded the greatest mortality is marked by the preliminary abortion, delivery, or discovery of the uterine pregnancy followed by rupture of the ectopic pregnancy. The mortality following this sequence of events has been high and in the neighborhood of 20 per cent. It is to this group that the new case reported belongs. Superficially this case resembles a postabortal infection. Only repeated examinations and the discovery of the disappearance of the pelvis mass led to laparotomy and the revelation of the true diagnosis.

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THE RESULTS OF SURGICAL CASTRATION IN WOMEN UNDER FORTY

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THE gynecologist, in operating upon women under forty, especially those suffering from chronic adnexal disease, often allows his choice of operative procedure to be influenced by a desire to preserve ovarian function, even though the question of future pregnancy is not involved. Thus, he may choose a less radical procedure and risks the possibility of the recurrence of symptoms because moderately diseased adnexa have not been removed.

What is the actual hazard of surgical castration in women under forty? In an effort to answer this question, a study of the results of surgical castration in women under forty was started at Bellevue Hospital in 1940. The scope of the investigation was to be wide enough to include answers to the following:

1. How often and how soon does the menopausal syndrome follow surgical castration?
2. How severe is the menopausal syndrome?
3. How long does the menopausal syndrome last?
4. What is the influence of surgical castration on libido?
5. How often does surgical castration precipitate the appearance of any other constitutional disease?
6. What is the influence of surgical castration on blood pressure?

At the outset, certain criteria were established:

1. All patients were to be under forty.
2. No woman was to have suffered symptoms of a spontaneous menopause before operation.
3. All cases were to be complete surgical castrates.
4. The minimal period of postoperative observation was to be three months.
5. No patient was to receive estrogenic therapy before a minimal period of six months of observation.
6. Estrogenic therapy was to be administered only if symptoms were not controlled by mild sedatives.
7. 150 mg. Hg systolic and 90 mg. Hg diastolic pressure was to be considered the upper limit of normal blood pressure.
8. A minimal fluctuation of 20 mg. Hg systolic and 15 mg. Hg diastolic pressure was required before a change in blood pressure was said to have occurred.

In the three years that this study has been carried on, 41 cases have been accumulated subscribing to the above prerequisites. Thirty-six of these women were colored and 5 white. The preponderance of colored patients was due to the fact that the most common reason for total cas-

tration was chronic adnexal disease, a much more prevalent affliction in the colored race at Bellevue Hospital.

The age group of the patients is shown in Table I. It will be noted that 71 per cent were under 35.

TABLE I. AGE GROUP

A. Less than 20	1	
B. 20 to 25	4	71%
C. 25 to 30	6	
D. 30 to 35	18	
E. 35 to 40	12	29%

It will be noted in Table II that 54 per cent of the patients were observed longer than a year.

TABEL II. DURATION OF OBSERVATION

From 3 to 6 months	6	
From 6 to 12 months	13	
From 12 to 18 months	10	
From 18 to 24 months	9	54%
From 24 to 36 months	3	

Thirty-five or 85 per cent of the cases had a precipitate menopause appearing immediately after castration. Six or 15 per cent had no symptoms whatsoever. The nature and severity of symptoms in the order of frequency are recorded in Table III.

TABLE III. NATURE AND SEVERITY OF MENOPAUSAL SYMPTOMS

	NONE	OCCASIONAL	MODERATE FREQUENCY	DISTRESSING
Flushes	16	21	7	7
Headaches	23	18	0	0
Insomnia	26	14	1	0
Dizziness	29	11	1	0
Arthralgia	33	8	0	0

As to libido, 36 or 88 per cent of these patients found no change. Three or 7 per cent found their libido diminished; whereas 2 or 5 per cent actually experienced an increase in libido.

It will be observed in Table IV that 50 per cent of the cases had their symptoms last less than 6 months, 75 per cent less than a year.

TABLE IV. DURATION OF MENOPAUSAL SYMPTOMS

A. Less than 3 months	10 or 25%
B. 3 to 6 months	11 or 25%
C. 6 to 12 months	10 or 25%
D. 12 to 24 months	6 or 15%
E. 24 to 36 months	4 or 10%

As far as the severity of symptoms was concerned, in only one case were menopausal symptoms sufficiently severe to be uncontrolled by barbiturates and to require estrogenic therapy. Thirty or 75 per cent were controlled with barbiturates; whereas 10 or almost 25 per cent required no therapy at all.

No patient in this series developed a constitutional disease, such as diabetes, arthritis, or thyrotoxicosis, following surgical castration. Only one woman of 35 developed a slight elevation of blood pressure. Her preoperative pressure was 138 mg. Hg systolic and 86 mg. Hg diastolic. Seen in the return clinic four weeks following her operation, her blood pressure was 164 mg. Hg systolic and 96 mg. Hg diastolic. It maintained approximately this level for the 4 months during which she was observed. Her menopausal symptoms were not severe and were controlled with barbiturates. Symptom-free, she failed to return for further checkup. This case merely points out the necessity of the continuation of such a study in a number of clinics so that many more cases can be accumulated and the incidence of hypertension following castration can be more accurately compared with the incidence of essential hypertension occurring in women of the same age who have not been castrated. The precipitate appearance of hypertension following the operation is not necessarily proof of its direct relationship.

Summary and Conclusions

From the careful observation and study of this small group of patients it can be assumed that:

1. Surgical castration results in the abrupt onset of the menopausal syndrome in 85 per cent of cases. In a minority (15 per cent) no evidence of this syndrome appears.

2. In the vast majority of instances the menopausal symptoms are not severe and do not require estrogenic therapy, being easily controlled by barbiturates.

3. The duration of such symptoms is usually brief; in 50 per cent of the patients being less than 6 months, and in 75 per cent, less than a year.

4. Libido is usually uninfluenced by this procedure, being diminished in 7 per cent, while in 5 per cent the patient actually experienced an increase in libido.

5. In no instance, did surgical castration precipitate the appearance of any constitutional disease.

6. In only one instance was surgical castration followed by evidence of hypertension. The relationship of this sequence is considered to be highly doubtful.

7. It is believed that the distressing aftereffects of surgical castration in relatively young women for justifiable indications are frequently exaggerated.

TREATMENT WITH PENICILLIN AFTER THE FAILURE OF SULFA DRUGS IN A CASE OF VAGINAL PLASTIC FOLLOWED BY BLOOD STREAM INFECTION*

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MRS. B. I., aged 49, was seen in consultation at a private hospital. The history was as follows: Gravida ii, para ii, suffered from rheumatic endocarditis, arteriosclerosis, hypertension and menopause. The family physician reports that her blood pressure was 212/98. Under treatment her blood pressure dropped to 148/78 and palpitation was relieved, but the protruding of the vagina, which could not be helped with a pessary, caused the family physician to refer her to a surgeon who did a repair of the enterocele. The record at the private hospital described the operation as a "Manchester," and further stated that following the operation the patient was well for a few days. Then her temperature rose to 105° F. She received an intravenous injection of glucose with sulfathiazole, temperature dropped to normal and remained so for a few days. Then the temperature rose again and the treatment was repeated with a similar reaction.

When the patient was first seen she was a very thin, hypertensive individual with slight vaginal oozing and a septic temperature curve. Vitamin K and transfusion were recommended for the bleeding. This treatment acted most favorably and after the temperature had been normal for four days, the patient was discharged from the institution. Shortly after her return home the high temperatures recurred and the patient seemed sicker than ever. Then at the request of the family and of the family doctor and the operating surgeon, she was admitted to the gynecological wards of the Lenox Hill Hospital. The history taken at the time of her admission, though most complete, adds nothing of importance to the story as here told.

On admission to the Lenox Hill she was acutely ill and had a temperature of 103.6° F., which rose the next day with a chill to 106.6° F. Careful examination revealed no cause for the temperature and the general condition, but the laboratory reported *Streptococcus hemolyticus* from blood culture on two successive examinations. We then naturally thought that we were pretty much at the end of our troubles and that we could cure the patient promptly. Therefore, sulfadiazine was started intravenously and by mouth and was pushed to the point where the sulfadiazine level in the blood was 66.6 mg. and the patient was passing only about 300 c.c. of urine though taking 2,500 c.c. by mouth and infusion, and sulfadiazine crystals were present in the urine. Despite this heroic treatment very little was gained. During the course of the illness five or six small transfusions were given. On the twentieth day after admission to the hospital, when the temperature was still between 103° F., and 105° F., the first dose of penicillin was given and continued as follows:

*Read at the meeting of the New York Academy of Medicine, Section on Gynecology and Obstetrics, October 26, 1943.

Forty thousand Oxford units daily for 7 days; the first 24 hours in a continuous intravenous saline drip and then intramuscular injections every 3 hours. The eighth to the eleventh day the dose was cut to 30,000 Oxford units daily, 5,000 given every 4 hours. Medication was given for 11 days with a total of 370,000 Oxford units.

In the first 36 hours the patient showed tremendous clinical improvement and the blood culture then gradually became sterile. On the forty-eighth day after admission to the hospital the patient was discharged seemingly cured, having had normal temperature for 14 days and a pulse that had gradually come down to normal.

During her stay at the hospital her basal metabolism rate was shown to be plus 6 per cent and the electrocardiograph reading was within normal limits. X-rays of the chest and abdomen were negative. The urine which at first showed bacteria and pus, hyaline and granular casts, also gradually improved under the treatment. When the patient was seen on October 6, she had a blood pressure of 192/106, her weight was 97½ pounds, which was about ten pounds under her normal, and the urine was negative. Except for general weakness everything was then satisfactory.

812 Park Avenue

ABDOMINAL PREGNANCY REQUIRING SECONDARY REMOVAL OF THE PLACENTA

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FEW patients with abdominal pregnancy require subsequent surgical removal of the placenta. In the absence of infection, it is usually agreed that the placenta left in the abdomen will become absorbed.[1, 2]

That this does not always occur is shown by the following report and two other cases found in the English literature of the past ten years. In 1940, Nicodemus and Carrigg[4] reported a case in which the placenta did not absorb but suppurated and became walled off from the peritoneal cavity. The placenta was subsequently removed from an abscess wall which localized in the right upper quadrant of the abdomen. The patient recovered. In 1940, Lull[3] reported a case of abdominal pregnancy in which the placenta did not absorb. Two months after the original laparotomy it was necessary to remove part of the large hemorrhagic cyst which had formed. The remainder of the cyst was closely adherent to the intestine and was marsupialized and packed. The patient made a good recovery.

Symptoms associated with nonsuppurative encapsulation of a retained abdominal placenta are recorded in the following report.

J. J., colored, aged 22, gravida ii, para i, was admitted to Gallinger Municipal Hospital on April 21, 1942, complaining of cramp-like pains in the upper abdomen. Her last normal menstrual period began November 25, 1941. This was followed by slight bleeding in December and January. For two weeks, she had experienced sharp, intermittent abdominal pain which had become quite severe on the day of admission. She had had no fainting or shoulder pain. Past history included an uncomplicated delivery of a full-term, living infant in 1938, and acute salpingitis in November, 1940.

On admission temperature was 98.6° F., pulse 112, respirations 20, and blood pressure 120/75. The abdomen was enlarged and diffusely tender. Fetal movements could be felt which coincided with the attacks of pain. Fetal heart sounds were present. The fundus of the uterus extended to the level of the umbilicus. The right round ligament was palpable. A firm, tender, ballotable mass beneath the left costal margin seemed to be attached to the fundus. The cervix was soft, blue, and closed. The cul-de-sac was clear.

A soft tissue x-ray of the abdomen showed a fetus of approximately seven months' gestation. It occupied the left side of the abdomen from the iliac crest to just beneath the diaphragm. There was no evidence of a uterine wall surrounding the fetus.

The blood Kahn and urinalysis were negative. Blood count showed hemoglobin of 88 per cent, erythrocytes 4,400,000, and leucocytes 10,600.

A preoperative diagnosis of abdominal pregnancy with ruptured membranes was made on April 22, 1942. A laparotomy was performed in which the uterus was found to be symmetrical, soft, and enlarged to the size of a four months' pregnancy. The right tube was not identified, but a mass 8 cm. in diameter, presumably a hematoma, was found in the right broad ligament. The placenta was firmly attached to the fundus of the uterus, to several loops of intestine, and to the mesentery. The

membranes had ruptured and the fetus was lying free in the abdominal cavity underneath the dome of the left diaphragm. A living 2 pound 15 ounce (1,333 grams) infant was delivered. The cord was ligated close to the placenta and cut. There was no appreciable bleeding. For fear of provoking hemorrhage and injuring the bowel, the placenta was left in situ and the abdomen closed. The infant died twelve hours after delivery.

The patient's postoperative course was afebrile. She was discharged on the twenty-seventh postoperative day.

On June 2, 1942, she complained of swelling and occasional pain in the abdomen. The abdominal scar was well healed. The body of the uterus was anterior and enlarged to twice normal size. A cystic mass, 10 cm. in diameter, rested on the right side of the fundus of the uterus.

On June 17, 1942, the patient was readmitted to the hospital complaining of severe lower abdominal pain, and vomiting of twelve hours' duration. Physical findings had not changed since the last clinic visit. The patient continued to vomit, developed shoulder pain, pallor, shifting dullness in the abdomen, and an acute anemia. She showed no signs of shock. Intra-abdominal bleeding from an old retained placenta was considered. She was treated with bed rest, sedation, blood transfusions, and supplemental vitamins. The acute symptoms subsided within a few days. A quantitative Aschheim-Zondek test was negative in all dilutions. She was discharged improved on her fourteenth hospital day.

She returned five days later with recurrent severe epigastric pain. These attacks continued to recur at irregular intervals. The mass in the abdomen seemed to be enlarging. On July 30, 1942, approximately three months after the delivery of the baby, an exploratory laparotomy was done. The lower abdomen was filled by a large cystic mass approximately 20 cm. in diameter. The cyst was completely encapsulated by the omentum and small and large bowel. The appendix was closely adherent to the cyst. The liver was not involved. The omentum was freed from the anterior wall of the cyst. In freeing several loops of bowel, incision was carried through the posterior wall of the cyst allowing approximately 500 c.c. of rust-colored fluid to escape. As soon as the bowel and the omentum were freed, the anatomical pathology became apparent. The uterus was small, anterior and well involuted. The placenta was closely adherent to the posterior and superior wall of the uterus. The bulbous, fimbriated end of the left tube and the ovary were attached to the cyst wall. The right tube was intimately attached to the cyst. The right infundibulopelvic ligament was hypertrophied and contained greatly enlarged vessels which had evidently been the source of the major blood supply to the placenta. A supracervical hysterectomy, bilateral salpingo-oophorectomy and appendectomy were done. The abdomen was closed without drainage.

The patient's postoperative course was uncomplicated. She was discharged on the thirteenth postoperative day.

Since her discharge from the hospital on August 12, 1942, the patient has gained 27 pounds. Hot flushes have been entirely relieved by estrogen substitution therapy. On January 28, 1943, six months after removal of the placenta, examination showed that the abdomen was well healed; the cervix was clean, well supported and closed; pelvis was entirely free of masses or tenderness.

Summary

A case of abdominal pregnancy requiring secondary removal of the placenta is reported. It is of interest that the placenta did not absorb or suppurate, but became encapsulated by the bowel and omentum. Subsequent abdominal symptoms became so severe that surgical intervention was undertaken. These were completely relieved by secondary removal of the placenta.

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Editorial

A Friendly Gesture

A RECENT announcement which should prove of interest to American obstetricians and gynecologists comes from England. It relates to the endowment of a lectureship by an anonymous donor, a Fellow of the Royal College of Obstetricians and Gynecologists. The interest from a fund of one thousand guineas is to be devoted to a lecture every second year alternately by a member of the Royal College on the subject of infertility and by an obstetrician or gynecologist from the United States on any topic selected by him. This would mean that an invitation to an American participant would be possible every fourth year and the honorarium would amount to about seventy pounds or the equivalent of some three hundred dollars.

The Royal College of Obstetricians and Gynecologists was founded in 1929 by W. Blair-Bell of Liverpool who was its first president with William Fletcher Shaw of Manchester as secretary. The latter, after having served as president for the past five years and being knighted, is now retiring from office and is being succeeded by Eardley Holland of London. The endowed lectureship commemorates Sir William Shaw's presidency and the anonymous donor wishes to demonstrate and further the friendship felt by our English colleagues toward the American profession. As such, it is worthy of our gratitude and appreciation. The postwar period with means of communication fully restored should witness the development of closer bonds between the great English-speaking countries. The interchange of ideas through the medium of personal contacts between groups interested in special branches of medicine can accomplish much, not only among the participants, but those whom they serve in a professional capacity. It is to be hoped that these objects may be possible of execution at an early date when the specter of war has been eliminated and opportunity offered again for more peaceful pursuits.

Department of Reviews and Abstracts

Selected Abstracts

Cesarean Section

Marin, J. de Jesus: A Probable Solution of the Eternal Problem of Uterine Suture in Classical Cesarean Operation, Rev. de cir. México **14**: 239, 1942.

J. de Jesus Marin has had 100 per cent satisfactory results in a series of fifty cases of classical cesarean section. The cases were entirely unselected and included those with ruptured bag of waters; patients in active labor; patients who had been examined several times; febrile cases; women with vertex, breech and shoulder presentations; and patients with previous cesarean sections. He ascribes the good results to the following factors: scrupulous preoperative preparation; thorough vaginal and peritoneal hygiene; protection of the abdominal cavity with pads of absorbent material, and strict adherence to his modified technique of uterine suture.

The author's method of uterine suture is as follows: The first row of sutures consists of heavy silk sutures inserted in the upper wound commissure, in the middle, and in the region of the lower commissure; between these sutures are inserted chromicized catgut No. 3 sutures spaced 2 cm. apart. These sutures take in all of the uterine wall with exclusion of the mucosa and the serosa. After all the sutures have been inserted the knots are tied firmly. The surface of this first row of sutures is then thoroughly disinfected. A continued chromicized catgut No. 2 suture is then anchored ½ cm. above the upper wound commissure. If the bag of waters had ruptured several hours before operation, and to prevent alarming postoperative distention, a warmed ampoule of 50 to 200 c.c. of amfetin (Lilly) is then poured into the abdominal cavity. Before closing the abdomen completely, a wick of braided silk is left for drainage of the cellular tissues, which is removed after 48 hours.

J. P. GREENHILL.

Perez, Manuel Luis, and Echevarria, Ramon: Prophylactic Intraperitoneal Sulfanilamide Therapy in Obstetric Surgery of Infected Cases, Bol. Soc. de obst. y ginec. de Buenos Aires **21**: 234, 1942.

Perez and Echevarria report the results in 11 patients. Their procedure was as follows: After opening the abdomen and performing cesarean section, sulfanilamide was distributed in the following areas: the uterine cavity, the cervicosegmental wound, the isthmus, and the suture line of the visceral peritoneum. Half or two-thirds of the drug was placed in the lower abdominal peritoneum, and finally some sulfanilamide was left in the subcutaneous cellular tissues. The dosage used was 4 Gm., except in frankly contaminated cases, where it was increased to 6 and 8 Gm. However, the latter dose proved excessive, for unfortunately, one patient died of sulfanilamide intoxication as shown by the findings on necropsy.

Although the results in such a small series are not conclusive, they were very gratifying, considering that all cases were suspected of infection or were frankly infected. In no case did peritonitis or any other significant septic process develop. There was only one case of subcutaneous cellular phlegmon and two of hematoma, one in the subcutaneous tissue, and the other in the broad ligament.

Owing to large doses of the drug in some cases there was elevated temperature, cyanosis of the face and extremities, and slight reduction in the red cell count and percentage of hemoglobin, for a few days. There were, however, no renal complications, and in one case the drug was used despite the presence of hypertension and 1.5 per cent albumin in the urine.

J. P. GREENHILL.

Kletzhändler, M.: Uterine Rupture After Cesarean Section, Monatsch. f. Geburtsh. u. Gynäk. **113**: 305, 1942.

In the Zurich Clinic from 1920 to 1938, there were 812 cesarean sections. During this time three uteri ruptured following cesarean sections performed in this clinic, and three additional cases of rupture of the uterine scar from operations performed elsewhere were also encountered.

The author reviewed 268 articles dealing with 402 cases of rupture of the uterus. In this review of the literature there were 141 ruptures of the scar following classical operations, 55 after the transverse fundal incision, 87 after the cervical longitudinal incision, 5 after the cervical transverse incision and in 104 cases information was not given.

About four-fifths of all the mothers were saved by operation and about the same proportion of babies died as a result of uterine ruptures. The same results were obtained with hysterectomy as with suture of the laceration.

J. P. GREENHILL.

Ribeiro, Eurico Branco: Intramural Pituitrin in Cesarean Operation, Bol. do Sanat. Sao Lucas **3**: 179, 1942.

Eurico Branco Ribeiro (Sanatorium Sao Lucas) had used intramural pituitrin for ten years with very satisfactory results. Contraction of the uterus follows immediately, separation of the placenta is facilitated, hemorrhage is greatly reduced, the operative field is cleansed, the visibility of the edges of the uterine incision is enhanced and suturing can be carried out with more precision and security; all these facts lead to a more speedy conclusion of the operation. The technique is simple. Before the operation the contents of two ampoules of pituitrin are drawn into a syringe and the injection held ready. Immediately after extraction of the fetus, the pituitrin is injected into the anterior wall of the uterus.

J. P. GREENHILL.

Bazul, Victor Manuel: Contribution to the Study of Segmental Cesarean Operation, Thesis for M.D. degree, Peru **1**: 189, 1941.

Victor Manuel Bazul discusses the history and indications of cesarean section and stresses the importance of the cervical method. He describes the extraperitoneal and transperitoneal methods, with their indications, disadvantages and complications, and cites a number of cases in which these methods were used. Cervical cesarean section is safest for mother and fetus. The method may be used in clean, suspected and infected cases without jeopardizing the general condition of the woman or exposing her to peritonitis. It allows the use of trial labor and avoids embryotomy of the living fetus. It permits the development of subsequent pregnancies without fear of uterine rupture. The extraperitoneal method is preferred despite the complexity of its technique, because of its excellent results: 13 cases gave no maternal mortality and a fetal mortality of 7.05 per cent. The transperitoneal method is the best for the practitioner because

of its simplicity: with the technique of Opitz, twenty-five cases gave a maternal and fetal mortality of 4 and 8 per cent respectively. Cervical cesarean section is now used in all the maternities of the world, and its diffusion in Peru will contribute to decrease the mortality rate of cesarean section.

J. P. GREENHILL.

Gonzalez, Juan B., and Cutuli: The Infected Case. Its Symptomatologic Concept and Significance as Basis for the Indication of Cesarean Section in the Presence of the Rights of Symphysiotomy, Bol. Soc. de Obst. y Ginec. de Buenos Aires **21:** 157, 1942.

Juan B. Gonzalez and Cutuli call attention to the reduction in the percentage of cesarean section for contracted pelvis in the native statistics which they studied. These statistics include 198 cases of symphysiotomy for contracted pelvis, with five deaths (2.52 per cent) 139, (70.20 per cent) were impure cases with one death (0.71 per cent) due to peritonitis. The 116 impure cases treated by laparotomy gave a maternal mortality of 13.82 per cent and a peritoneal infection rate of 6.03 per cent; in 56 of these cases, the indication for laparotomy was disproportion between the pelvis and fetal head: the maternal mortality was 10.71 per cent and the peritoneal infection rate, 7.14 per cent. This shows the superiority of symphysiotomy over all modern methods of cesarean section in the treatment of relative bony dystocia. These comparative figures should be of special interest to foreign schools which admit that cephalopelvic disproportion constitutes from 55 to 75 per cent of their indications for cesarean section.

J. P. GREENHILL.

Leon, J.: Artificial Extraperitoneal Cesarean Section. Author's technique, Arch. Clin. obst. y ginec. **1:** 402, 1942.

Leon adds twenty-one more cases of his own extraperitoneal cesarean section to the twenty already reported. The uncorrected maternal mortality was 10.2 per cent which is satisfactory considering that many of the patients were frankly infected. The fetal death rate was 7.3 per cent.

J. P. GREENHILL.

Thomas, Rufus C.: Cesarean Section Under Spinal Analgesia, J. Obst. & Gynaec. Brit. Emp. **49:** 3, p. 247, 1942.

The author mentions that the ideal anesthetic in cesarean section is the one which carries the highest degree of safety to mother and child and is also the one which offers the maximum operative comfort to the surgeon. The child is unaffected by the anesthetic and any marked degree of asphyxia is rare. The operation is made easier for the surgeon because of the marked relaxation. Spinal anesthesia does not interfere with satisfactory uterine contractions. The author reviews the literature on the subject and quotes the various arguments for and against spinal anesthesia in cesarean section.

In his own cases (121) Thomas used percaine (Ciba). Atropine gr. $\frac{1}{100}$ and ephedrine gr. $\frac{3}{4}$ were given preoperatively. Where the patient had a test of labor under twilight, section was not carried out under two hours after the last medication. Mental tranquility of the patient is of utmost importance. In cases of placenta previa, the patient should be held by an attendant for the injection to prevent any increase in intra-abdominal pressure which might cause bleeding.

Two patients developed headaches which after spinal anesthesia persisted for several days. Three developed chest complications; four thrombophlebitis. Post-

operative distention was rare and there were no cases of secondary hemorrhage. Five patients had 2 sections under spinal anesthesia. One death occurred on the ninth postoperative day from pulmonary embolism.

WILLIAM BERMAN.

Obstetric Operation—Cesarean

Pla, P., and Ricci, G.: Spinal Anesthesia in Cesarean Section, Bol. soc. de obst. y ginec. de Buenos Aires **20:** 817, 1941.

The authors state that patients are now carefully selected to insure maximal safety in spinal anesthesia: those with disease of the nervous system, syphilis, pernicious anemia, marked hypertension or hypotension, labile circulation, shock and hemorrhagic conditions are excluded. Patients, who have lost blood but have a normal blood pressure and no signs of shock, must be added to this list. The technical conditions to be observed are premedication with ephetonine, morphine and atropine, sitting position, low puncture, smallest possible amount of anesthetic, allowance of necessary time for fixation of the anesthetic and only then decubitus and careful change to Trendelenburg position if indicated; twenty minutes later, another injection of ephetonine to prevent the fall of blood pressure so characteristic of this anesthesia. Nevertheless, some unpredictable accidents still occur.

From 1934 to 1941, the authors used spinal anesthesia in 45 cesarean sections. Among 36 cases, the anesthetic was tutocain in 23, novocain in 9, percain in 3 and meticain in one. Therefore, there were six serious accidents with three deaths by bulbar syncope: one each with tutocain, novocain and meticain anesthesia. This is a high mortality, which becomes even more significant by comparison with the number of daily operations for gynecologic disorders in which the same anesthetic technique is used without fatality. The accidents suggest the possibility of a special susceptibility of the pregnant woman for spinal anesthesia and particularly for novocain or other compound of this type. The accidents were characterized by rapid diffusion of the anesthetic, cyanosis, arrest of breathing thread-like pulse, hypotension and syncope. The symptoms did not respond to oxygen-carbon, ephetonine, coramine or other emergency medication. One patient died during the operation and the other two lingered on for four days without recovering from the hypotensive adynamic condition caused by the anesthetic.

The authors restrict spinal anesthesia to ideal cases of obstetric surgery and prefer the use of tutocain which, in 0.03 to 0.05 Gm. doses, gives optimal results.

J. P. GREENHILL.

Endocrinology

Kern, E. S.: Prothrombin in Mother and Child: Investigation of the Prothrombin Content of the Mother's Blood in Pregnancy, Labor and the Puerperium as Well as in the Newborn; the Role of Vitamin K in Obstetrics, Monatschr. f. Geburtsh. u. Gynäk. **114:** 47, 1942.

The author's investigations showed that the prothrombin content of the blood of normal women in the first few months of pregnancy varies from 103 to 113 per cent. From the fifth month until the end of pregnancy the prothrombin content rises and attains a maximum of 134 per cent in the tenth month. During labor it falls to 116 per cent and rises again during the puerperium without, however, reaching the high point of 134 per cent.

The prothrombin content of the newborn is about 60 per cent. There is no direct relationship between the maternal and the infant prothrombin content.

The variations in the maternal prothrombin content during pregnancy and the diminished prothrombin content in the infant, are probably due more to endogenous factors than to variations in the intake of vitamin K.

J. P. GREENHILL.

Jones, G. E. Seegar, and TeLinde, R. W.: An Evaluation of Progesterone Therapy in the Treatment of Endometrial Hyperplasia, Bull. of the Johns Hopkins Hosp. 71: 5, 282, 1942.

The authors have considered the following facts for the successful use of progesterone in the treatment of endometrial hyperplasia:

1. Progesterone as substitution therapy and associated endocrine abnormalities which may be contributing factors in the disease must be investigated.

2. The dosage and time interval of administration must be adequate.

3. Progesterone is not useful in checking immediate hemorrhage. It is used for preventive purposes and must generally be continued cyclically over a period of at least four months.

4. A recurrence of the disorder will not be prevented by progesterone. Hormone studies performed on a selected group of cases showed no pregnandiol in the urine before treatment, and no excessive urinary gonadotropin. Estrogen values were within the normal range.

C. O. MALAND.

Heckel, George P.: The Estrogen Sparing Effect of Hysterectomy, Surg., Gynec. & Obst. **75:** 379, 1942.

The author was able to demonstrate that corpora lutea of pseudopregnancy in the rabbit may be prolonged by the removal of the uterus. Furthermore, an amount of estrogen insufficient to prolong the corpus luteum will achieve this effect if a sufficient amount of the uterus has been removed. Based on the supposition that the uterus uses this substance, the author hypothesizes that hysterectomy produces an estrogen sparing effect.

L. M. HELLMAN.

Brewer, John I., Jones, Harold O., and Skiles, J. H.: Effect of Gonadotropic Substance on Ovulation, J. A. M. A. **118:** 278, 1942.

The authors report their experiences in the use of pregnant mare serum. The injections were given intramuscularly throughout the entire course. The patients treated were all to be operated upon later. Half of the group were operated upon in the first half of their menstrual cycle. The second group was operated upon in the second half of the cycle. An untreated group of patients was used as control. In the treated group of twenty-four patients, thirteen possessed corpora lutea of the current cycle. A microscopic study of eleven of these thirteen patients indicates definitely that ovulation could not have occurred as a result of the intramuscular injection of the gonadotropic substance. In the control group of twenty-two patients, sixteen patients possessed corpora lutea of the present cycle. There was no demonstrable increase in ovulation in the treated group. Ovulation was not induced in the treated patients either early or late in the cycle. The simultaneous induction of ovulation of more than one follicle was not brought about as a result of the therapy. An attempt failed to induce ovulation before or after spontaneous ovulation.

WILLIAM BERMAN.

Gynecology

Arenas, N., and Roganti, A.: Unusual Evolution of Pyosalpinx, An. del Inst. de mat. y Asis. Soc. (Buenos Aires) **3**: 1941.

A thorough discussion of pyosalpinx accompanies the protocol of the authors' interesting case of a young woman who was hospitalized shortly after marriage with bilateral pyosalpinx. One of the abscesses spontaneously opened into the rectum. Abdominal palpation revealed a large mass in the right iliac fossa. Expectant treatment was followed for approximately two months while the mass increased in size. At length, a 4 cm. incision was made over the most central and fluctuating part of the abscess, with abundant drainage and subsequent recovery of the patient.

ROBERT J. WEISSMAN.

Brines, Osborne A., and Blain, James H.: Adenomyosis of the Uterus, Surg. Gynec. & Obst. **76**: 197, 1943.

The authors report a ten years' study of adenomyosis during which period 73 cases were observed. This represented an incidence of 10.7 per cent of all the uteri removed. A brief review of the literature is given and the confusion in the existing terminology pointed out. The authors emphasize that, strictly, adenomyosis is defined as the occurrence of heterotropic endometrium within the myometrium, unassociated with tumor formation. There may or may not be a general hyperplasia of the myometrium, and there generally is a slight nodularity of this layer. It is stated that this condition is thus differentiated from adenomyoma on one hand, and endometriosis on the other. The location of the islands of endometrial tissue, more frequently on the inner half of the uterine wall would suggest invasion as the mechanism of production, however, by means of special stains and a consideration of the embryogenesis, the authors reach the conclusion that the aberrant endometrial islands are derived from dedifferentiated myometrial cells capable of forming endometrial stroma or glands. Adenomyosis can definitely be said to be benign.

L. M. HELLMAN.

Black, Elinor F. E.: The Use of Testosterone Propionate in Gynecology, Canad. M. A. J. **47**: 124, 1942.

Case reports are cited to illustrate the use of testosterone propionate in gynecology. The indications given are menorrhagia, glandular hyperplasia of the endometrium, menopausal bleeding due to glandular hyperplasia of the endometrium and small uterine fibroids, mastalgia, and inhibition of lactation. In the presence of a fibroid in a young man, testosterone propionate failed to control bleeding.

The author emphasizes that cases must be carefully chosen and that such conditions as retained products of conception, uterine and cervical polyps and malignancies must be ruled out. Preliminary curettage is often necessary. The tendency to masculinization must not be minimized even though this effect is transient.

CARL P. HUBER.

Endometriosis

Salaber, Juan A., and Nogues, Armando E.: Uterine Isthmic Endometriosis Perforating Into the Parametrium, Bol. soc. de obst. y ginec. de Buenos Aires **20**: 770, 1941.

The authors state that the incidence of endometriosis of the genital system is increasing, but that endometriosis of the parametrium is relatively rare. It may be primary or secondary. Clinically, endometriosis of the broad ligament occurs

as a slightly movable or fixed tumor, a more or less diffuse infiltration of the cellular tissue of the parametrium which acquires a hard, ligneous consistency. It is sensitive to pressure and its symptoms become more marked during menstruation. Painful dysmenorrhea is the constant and outstanding symptom of this form of endometriosis and presents the clinical characters described by Hunner in strictures of the pelvic ureter due to compression by infiltrating pathologic processes of the parametrial tissues. In localization and irradiation, the pain resembles the colic of a passing calculus, but it varies in intensity and extension; it is usually described as severe, diffuse, local and lateral; it may begin one week before menstruation and persist with varying severity until menses are established, or it may coincide exactly with menstruation. The clinical character of the dysmenorrhea and the disappearance of the latter with the elimination of the ureteral stricture suggest that the pain is due to premenstrual congestion which increases the ureteral stenosis and the volume of the tumor tissue. This interpretation is supported by the authors' case in which the pain was relieved after menstruation and exacerbated at the following menstruation before operation. Treatment must be radical because of the impossibility of extirpating all the involved tissue. An important point is ample liberation of the ureter from all compressing tissues to eliminate the dilatation of the ureter and renal pelvis.

J. P. GREENHILL.

Jessing, A.: Perineal Endometriosis After Prolapse Operation, Acta. obstet. et gynec. Scandinav. **112**: 225, 1941.

Jessing reports a case of perineal endometriosis which occurred after a prolapse operation. It is assumed that the lesion arose from implantation during the operation because the uterus was curetted immediately before the prolapse operation.

J. P. GREENHILL.

Stephenson, R. T., and Graffagnino, P.: Endometriosis: A Problem of Treatment, South. M. J. **35**: 525, 1942.

A survey of the files of the Charity Hospital of New Orleans for a four-year period during which there were approximately 24,000 admissions, revealed only forty-two cases of endometriosis. This is a very small number for so large an institution. The racial incidence of eighteen colored patients and twenty-four white patients is disproportionate to the Negro-white ratio of gynecologic admissions.

Seven patients were unmarried; of the remaining, seventeen were sterile and eighteen were parous. The age incidence varied between 20 and 55 years, the greatest number occurring in the later functional years. Endometriosis was the primary pathologic condition in twenty patients, while in twenty-two there were other associated conditions. Fourteen patients, thirteen of whom were colored, also had "fibroids." Three patients, all colored, had chronic pelvic inflammatory disease.

Pain, which is the symptom most frequently encountered, occurred in twenty-five cases; in thirteen of these, endometriosis was the principal pelvic condition. It was not related to menstruation in fifteen instances, while in the others, the time relation was variable. The most frequent pelvic physical findings, which occurred either alone or in combination, were, uterine displacement, fixation, prolapse, and adnexal masses. Except for a single case in which involvement of the sigmoid colon occurred, the distribution of ectopic endometrium was limited to the pelvic organs; in three patients it was generalized in the pelvis.

The diagnosis may be easy or difficult. Where the characteristic nodules may be palpated in the vaginal wall, it is fairly obvious. The condition should be suspected when dense pelvic adhesions are encountered in the absence of typical

history and other findings of pelvic inflammatory disease. Under the same circumstances the diagnosis is strongly suggested by a complaint of acquired dysmenorrhea which becomes progressively worse. In five of the twenty primary cases of endometriosis, the diagnosis was made at operation, and, in the other five cases, histopathologic confirmation was required.

The only certain method of cure is removal of ovarian tissue. Treatment must be individualized. Factors to be considered when therapy is planned are, the age and economic status of the patient, the degree of the pathologic process, and the desire for children. In the older patients there is less indication for conservatism. Radical operation was performed in the twenty-two patients in whom there was associated pelvic disease, the latter condition, of itself, constituting an indication for the procedure. Of the twenty patients whose primary pelvic condition was endometriosis, fifteen were treated by radical surgery; conservative procedures consisting of partial oophorectomy and cauterization of endometrial transplants were employed in four patients. One patient refused any surgical treatment and was referred to clinic.

ARNOLD GOLDBERGER.

Extrauterine Pregnancy

Olivier, Claude: Cullen's Sign, Presse méd. 48: 593, 1940.

The author describes an obscure case of an ectopic pregnancy resulting in tubal abortion with minimal intra-abdominal bleeding. The only positive clinical finding other than a small palpable juxtauterine mass was a positive Cullen Sign.

The writer reviews the literature on the history and significance of circumnavel cutaneous discolorations. He credits Hofstatter, who reported such a condition in 1909 following surgery, as the first to report such a sign but admits that Cullen was the first to utilize the sign as a preoperative indication of hemoperitoneum.

The author concludes that Cullen's Sign is of rare but nonetheless significant value as a supplemental aid to diagnosis in atypical cases of hemoperitoneum.

CLAIR E. FOLSOME.

Menopause

Gessler, G.: The Influence of Folliculin Injections Upon the Glycemia of Postmenopausal Diabetic Women, Presse méd. 48: 780, 1940.

Large doses of estradiol benzoate were given, hypodermically, to four postmenopausal diabetic women. In two cases where the diabetes appeared first during the advent of the menopause, the follicular hormone provoked an early decrease in their glycemia. This decrease in the glycemia persisted only several days following the last hormone treatment. In two other cases, where the diabetes and menopause did not occur simultaneously, the decrease of glycemia with use of estradiol benzoate was not as constant.

The author explains the different responses to treatment by reasoning that in the former two cases the diabetes was, in part, of hypophyseal origin: that the hypersecretion of the gonadotropic hormone induces in these cases an "exaggerated diabetogenic factor"; and that injections of the follicular hormone inhibit the gonadotropic hormone to thus lower indirectly the glycemic level. In the latter two cases, where the diabetes and menopause did not occur at the same time, the anterior pituitary did not contribute to the etiology of the patients' diabetic conditions. The author notes that it requires at least 5 mg. of estradiol

benzoate to produce a lowering of the glycemia. He concludes that basal metabolism is little affected by the use of estradiol benzoate.

CLAIR E. FOLSOME.

Physiology of Pregnancy

Tapernoux, F.: The Qualitative Relationships of the Aschheim-Zondek Reaction at the End of Pregnancy and in the Puerperium, Monatschr. f. Geburtsh. u. Gynäk. **113**: 233, 1942.

The author found that in the presence of intrauterine fetal death, there are great differences in the excretion of the gonadotropic hormone. Occasionally Reaction I of the Aschheim-Zondek test remains positive for many months after fetal death. In four cases, Aschheim-Zondek tests were performed at the end of pregnancy and in the puerperium, and the genitalia of the mice used for the biologic tests were studied microscopically. The author found that there was an early disappearance of Reactions II and III. He emphasizes that quantitative factors of the test are important.

J. P. GREENHILL.

Del Castillo, E. B., and Pasqualini, R. Q.: Diabetes Insipidus During Pregnancy and After Castration, Médicina, México **2**: 335, 1942.

The authors describe two cases. The first woman had two normal pregnancies which did not change the diuresis, or influence the amount of posterior hypophyseal lobe powder required to maintain the diuresis within normal limits. The second woman had diabetes insipidus since she was 18 and underwent a bilateral ovariectomy at the age of 36, which had no effect on the polyuria; 150,000 international units of estradiol benzoate given in one week were also without effect. Accordingly, diabetes insipidus is independent of pregnancy and castration and is uninfluenced by the estrogens. Nasal aspiration of powder of posterior hypophyseal lobe produced a satisfactory reduction of the diuresis in both cases. Finally, implantation of bovine posterior lobe in the first case produced an antidiuretic action lasting three months, and an injection of five vasopressor units of pitressin tannate in oil in the second case, had an antidiuretic effect for about 48 hours, while 10 units acted satisfactorily for seven days.

J. P. GREENHILL.

Diagnosis of Pregnancy

Goldman, Lester M., Kessler, Henry B., and Wilder, Mildred E.: The Colostrum Cutaneous Test for the Diagnosis of Pregnancy, J. A. M. A. **119**: 130, 1942.

A group of 185 tests on antepartum cases were analyzed. One hundred and thirty-one, or 70.8 per cent, showed a negative reaction indicative of pregnancy, while fifty-four, or 29.2 per cent, showed a positive reaction. The period of gestation in those giving a correct response ranged from 9 to 39 weeks. In the post-partum group of 30 tests, there were 17 correct reactions or 56.6 per cent and 13 incorrect or 43.4 per cent.

In the control group the total number of cases performed was 153. The total number of correct reactions among this group was 103 or 67.3 per cent. This latter group included 40 men.

All together the authors' series showed about 70 per cent of all pregnancies had no sensitivity, while about 70 per cent of all nonpregnancies showed a reaction of sensitivity. It is therefore felt that in the authors' hands the colostrum cutaneous test does not appear to offer a valuable diagnostic procedure for pregnancy.

WILLIAM BERMAN.

Verhage, J. C.: The Significance of Ketonemia and Ketonuria in Pregnancy, Monatschr. f. Geburtsh. u. Gynäk. **113**: 1, 1942.

No rise in the amount of ketone bodies of the blood was found in pregnancy. When ketonemia is found during pregnancy or labor especially when it occurs in women with hyperemesis, it is the result of insufficient food intake. The rise in the amount of ketone bodies in the blood and urine as a result of starvation varies considerably in pregnant women. Ketonemia and ketonuria quickly disappear after sufficient intake of food.

J. P. GREENHILL.

Balbi, J.: The Question of Clinical and Roentgenologic Evaluation of Overterm Pregnancy, Monatschr. f. Geburtsh. u. Gynäk. **113**: 121, 1942.

The author attempted to discover signs which would reveal definite postmaturity. He came to the conclusion that there was only one way of deciding that a normal period of pregnancy had been passed. The criterion is the size of the abdomen. If the abdomen does not increase in size, or if it decreases after the calculated date, we may assume that pregnancy is going beyond term. The size of the child cannot be used as a criterion. Likewise, roentgenologically, the ossification centers of the bones cannot be used to judge the duration of pregnancy.

J. P. GREENHILL.

Fontava, G.: The Mineral Composition of the Bones in Pregnancy, Monatschr. f. Geburtsh. u. Gynäk. **113**: 57, 1942.

Investigation of the mineral composition of the femurs of pregnant guinea pigs showed that there is very little change in the calcium phosphate content during various stages of pregnancy. The number of young play no role. The author maintains that the minerals necessary for the development of the fetal skeleton under physiologic conditions are derived from the nourishment from the mother. The maternal bone reserves are not tapped.

J. P. GREENHILL.

Placenta

Bickers, William: "The Placenta: A Modified Arteriovenous Fistula," South. M. J. **35**: 593, 1942.

Burwell first suggested that most of the circulatory alterations occurring during pregnancy could be explained by assuming the placenta to be a modified arteriovenous fistula. The author repeated his work on the femoral venous pressures in pregnancy and made some original observations which confirm Burwell's thesis. The anatomic and physiologic basis for this concept is briefly outlined.

In a series of twenty-three primigravid patients, the femoral venous pressures and arm pressure were measured in the last weeks of pregnancy, the determinations being made on the same day. The results were correlated with the presence of lower extremity edema, which was measured with a centimeter tape, and with the site of placental attachment as determined by intrauterine palpation at the completion of the second stage of labor. Labor started spontaneously in all the patients, and, with the single exception of cesarean section performed for central placenta previa, delivery was accomplished by outlet forceps.

Whereas, in nonpregnant women, venous pressures in the arms and legs are approximately the same, in pregnancy the venous pressure of the lower extremities averages 100 to 150 mm. higher than that of the arm. This cannot be ex-

plained by the mechanical effect of the enlarged uterus. When the swelling of the ankles was unequal, it was noted that the edema was greatest on the side where the placental bruit was most distinct, and, that the femoral venous pressure was greatest on the same side.

Eight patients had clinical edema and the average femoral venous pressure exceeded that in the arm by 120 mm. (H_2O); in the nonedematous group, the average difference was 100 mm. The most frequent placental sites are, first, the posterior uterine wall; next, the lateral walls. In the twelve instances in which the placenta was implanted either anteriorly or posteriorly, the femoral venous pressures were approximately equal, as was ankle edema. The remaining two placentas were attached laterally, and the femoral venous pressure on the corresponding side averaged 28 mm. higher than that on the opposite side. The greatest venous pressure difference upper and lower extremity occurred in the patient with placenta previa; here the highest femoral venous pressure was recorded (260 mm.). The action of the placenta as an arteriovenous fistula is the only explanation for these observations.

ARNOLD GOLDBERGER.

Sterility, Fertility, Contraceptives

Dorn, Harold F.: The Potential Rate of Increase of the Population of the United States, Am. J. Soc. **48:** 173, Sept., 1942.

Dorn, of the U.S.P.H.S., states, after a review of late government statistics at the National Health Institute, it can be demonstrated that the fertility and mortality of the population of the United States, during the eleven-year period ending with 1941, was at least sufficient to maintain a stationary and possibly a slowly increasing population.

It is estimated now that probably 93 to 94 per cent of the white births and from 80 to 87 per cent of the colored births are registered. Dorn predicts that it may be stated, with considerable confidence, that the birth rate in 1943 and perhaps that for 1942 will be lower than the rate in 1941. *(U. S. Division of Vital Statistics provisional figure for the first 6 months of 1942 was 19.7 per 1,000.)*

Marriage and birth rates decreased rapidly after the 1929 depression, but the deficit in marriages was wiped out by the end of 1940. The average annual number of marriages (1921 to 1930) was 1,185,000 which increased to 1,284,000 (1931 to 1940). By the end of 1941, there will likely be an "excess" instead of a deficit in marriages.

The Selective Service Act's enactment in September, 1940, and the declaration of war in December, 1941, increased the number of marriages which would, in ordinary times, have been postponed for several months or even years. The increase in marriages in 1941, however, was most likely resultant from increased industrial activity. As would be expected, the increase in the birth rate (7.8 per cent higher for the first 4 months of 1942, compared to the corresponding 4 months of 1941) increased following enactment of the Selective Service Act. Our greatest decline in birth rate will not come probably until large expeditionary forces are sent overseas.

The reproduction for the white population (1930 to 1941) was approximately 100, while that for the nonwhite population was definitely above the replacement level. The increase in the crude birth rate, since 1933, has resulted almost entirely from an increase in the number of the first and second births and does not represent an increase in the lifetime fertility of women in the childbearing ages.

CLAIR E. FOLSOME.

Pineda, Rafael: Kymographic Insufflation in Female Sterility, An. brasil. de ginec. **13**: 265, 1942.

Pineda describes the Rubin apparatus and technique, and lists the indications, contraindications and dangers of the method as stated by Rubin. He has used the insufflation technique in one hundred patients during the past six months. To date, five pregnancies occurred in cases with primary sterility (in one of which it extended over 17 years and in two over five years), and two pregnancies in secondary sterility.

J. P. GREENHILL.

Lastra, Enrique Thwaites, and Jakob, Alfredo: Results of Surgical Treatment of Sterility, Bol. soc. de obst. y ginec. de Buenos Aires **21**: 327-331, 1942.

Enrique Thwaites Lastra and Alfredo Jakob report that following plastic operations on the tubes four of ten patients became pregnant. Three had full-term pregnancies and one had an ectopic pregnancy. The authors think the reason for their success lies in the fact that they operated only on clean cases, i.e., the patients had more or less healthy ovaries, they had no adhesions and the sterility was due to occlusion of the tubes in the isthmic region while the fimbriae were normal. The technique consisted of extirpation of the occluded portion and reimplantation of the tube as far as the uterine cavity. All patients with occlusion in the isthmic region are advised to submit to the operation if they desire to have children, but success is not guaranteed. Postoperative care is important; hysterography must be performed.

J. P. GREENHILL.

Jaffe, A. J.: Urbanization and Fertility, Am. J. Soc. **48**: 48, 1942.

In an extensive study of the relationship of urban to rural fertility, in which the rural fertility for a given area was given an index of 100, comparative urban areas had fertility indices as low as 50. The author is not inclined to give too much weight to contraceptive practice as a factor in reducing urban fertility. Abortion, sexual difficulties, legal restrictions and postponement of marriage as well as the practice of infanticide in some areas, all apply to affect the fertility rate. The potential number of children the average woman can bear is well in excess of 6 or 7, and it is evident that some form of birth control is practiced even in remote areas having available statistics where modern contraceptive techniques were not available. Fertility rate falls with increased desire for a better standard of living in any given group.

R. J. WEISSMAN.

Guttmacher, A. F.: The Contraceptive Clinic and Preventive Medicine, Human Fertil. **7**: 1, 1942.

The author feels it is the function of the contraceptive clinic to implement the more positive medical contraindications to pregnancy such as are found in women having heart disease, diabetes, tuberculosis, etc., as well as in psychotics and epileptics. The fact that the indigent and mentally defective are invidiously exceeding in reproduction those of normal mentality is not generally appreciated. Careful pelvic examination in the clinics is a new source of material for early diagnosis of malignancy as well as other conditions requiring medical or surgical attention. Finally, says the author, there is no reason why treatment of sterility should not be an equally important function of these clinics.

R. J. WEISSMAN.

Vaginal Infections

Woodruff, J. D., and TeLinde, R. W.: The Treatment of Gonococcal Vaginitis in Children With Diethylstilbestrol, South. M. J. **35:** 389, 1942.

Because of the fact that most cases of gonococcal vaginitis are treated in free clinics, and, that the cost of estrogenic hormone derived from natural sources and so successfully employed in treatment, is high, the authors resorted to the use of the synthetic hormone diethylstilbestrol.

Fifty consecutive patients, forty colored and ten white, were treated orally or by vaginal suppositories, and the results compared. The routine of treatment required weekly observation with smears stained by the gram method. This was continued until 3 consecutive negative smears were obtained. Cultures were made before, during, and after treatment, and weekly saline vaginal washings were examined for the relative number of pus and epithelial cells. Following the termination of therapy results were checked at two and at six weeks' period, and subsequently at four to twelve months.

While the percentage of negative smears at the end of two weeks of treatment was about the same for both modes of administration of the hormone, the results were more uniformly successful and generally obtained with greater rapidity when suppositories were employed. For the latter, a dose of 0.1 mg. is recommended. The optimum oral dose was 1 mg. per day. Toxic symptoms occurred when 1 mg. was given three times daily, while 0.1 mg. per day, was inadequate.

Whereas, breast enlargement occurred in approximately 46 per cent of the suppository group of cases, and regressed in from four to six weeks, it developed in 94 per cent of the oral series, and in two instances required about four months to disappear. Other side effects occurred only in the latter group and included, uterine enlargement, the development of pubic and axillary hair, enlargement of the clitoris and vaginal bleeding. No evidence of "vaginal fixation" was noted, and the authors were of the opinion that the insertion of a suppository by the child's mother or nurse was less disturbing than the taking of smears by the physician. They are emphatically in favor of the suppository method and prefer it to oral administration for the reasons expressed.

ARNOLD GOLDBERGER.

Russ, J. D., G. Collins, Conrad, F.A.C.S., and Powell, Sam: Prepuberal Vulvovaginitis, Clinics **1:** 117, 1942.

Prepuberal vulvovaginitis is discussed from the standpoint of physiology, pathology, diagnosis, criteria of cure, mode of transmission, and therapy. The introduction of estrogenic therapy represented a decided improvement over the use of antiseptics in the form of instillations, ointments, and douches. The authors have been impressed favorably with their results from the oral use of the synthetic estrogen, stilbestrol. They recommend 1 mg. crushed in milk given three times a day, orally. By the end of the fifth to seventh day of medication, vaginal smears show the absence of pus cells, absence of gonorrheal organisms, and the presence of a cornified adult type of vaginal epithelium. Biopsy of the infant vagina shows that this adult cornification remains about three or four weeks after discontinuation of the therapy. During the course of therapy, slight enlargement of the nipples and labia occurred, but these changes returned to normal and no untoward reactions were noted.

Apparently the oral administration of stilbestrol brings about the same local changes in the vagina which occur from the use of estrogens given in the form of vaginal suppositories.

HOWARD C. MOLOY.

Correspondence

Treatment of Deficient Spermatogenesis

To the Editor:

Although in agreement with most of the facts contained in the letter by Dr. Abner L. Weisman in the October, 1943, issue of the JOURNAL (page 618), I am not in accord with the following statement. Dr. Weisman states, "Can we stimulate spermatogenesis where it has faltered? It is almost universally agreed that in azoospermia, endocrines and the like, have failed miserably in the treatment of deficient spermatogenesis." Except in cases of double occlusion of the male genital tubes, I have never failed to bring about an improvement and in many cases a cure of deficient spermatogenesis by the use of the anterior lobe of pituitary gland extract in large doses and given by mouth for a period of six months or less. I prescribe 80 grains a day (16 five-grain tablets). The expense to the patient is very large but it is important to give it in these very large doses and to achieve a result.

MAX HUHNER, M.D.

88 CENTRAL PARK WEST

ANNOUNCEMENT

The Registry of Ovarian Tumors

About one year ago announcement was made of the fact that the American Gynecological Society had undertaken the sponsorship of an American Registry of Ovarian Tumors, and that it had appointed from its Fellows a committee of five gynecologic pathologists to carry on this work. Gynecologists and pathologists were urged to send material from unusual ovarian tumors to this Committee for study and classification, with the hope that an intensive and cumulative study of this sort would in time throw much needed light upon the pathology, clinical characteristics and perhaps even the histogenesis of some of the still poorly understood tumor types encountered in the ovary.

The response to this first announcement has been gratifying, but it is obvious that it escaped the notice of many readers of the JOURNAL, and that many of those who saw it have not realized the potential value of a concerted study of this sort. We are, therefore, making this second plea for the cooperation of clinicians and pathologists throughout the country. Heads of gynecological departments and pathological laboratories especially are asked to see to it that slides or tissue from all interesting and unusual ovarian tumors are sent to the Committee, together with an adequate clinical history, including such essential data as the patient's age, menstrual and marital history, operative findings and procedures, together with a gross description of the tumor, and photographs, should these be available. If the gross specimen or blocks of tissue are sent, they should be fixed in 10 per cent formalin. Where only slides are available, these should be carefully packed in wooden or metal slide containers to avoid breakage in the mails.

It should again be emphasized that the function of the Committee is not to render a purely diagnostic service, and that quick reports as to its collective opinion are not possible because of the time consumed in passing the material between the members of the Committee, scattered as they are in various parts of the country. When the study of the material submitted is complete, the contributors will be notified as to the final classification of the tumors in the Registry.

Since there is still much uncertainty as to the prognosis of certain tumors of the ovary, it is hoped also that information can be accumulated as to the subsequent course of the patients, particularly those with tumors of malignant or doubtful nature. To facilitate such a follow-up study, those who send in material are asked to supply the name of the attending surgeon or family physician, so that subsequent information as to the clinical course may be obtainable.

The Registry is to be looked upon as a cooperative project among the gynecologists and pathologists of this country, and it is earnestly hoped that all will develop the routine of sending material from all interesting ovarian tumors, with the above indicated data, to the Committee for study and registry. This material should be mailed to Dr. Emil Novak, Laboratory of Gynecological Pathology, Johns Hopkins Hospital, Baltimore, Md.

EMIL NOVAK, CHAIRMAN
ROBERT MEYER
HERBERT F. TRAUT
GEORGE H. GARDNER
KARL H. MARTZLOFF

Items

Progress of The E. M. I. C.

It may be of interest to note, as announced by the Federal Children's Bureau, that the total number of maternity and pediatric cases for which care has been authorized from the funds appropriated by Congress for this purpose through October 31, 1943, is 99,336. Five states, Connecticut, Colorado, Louisiana, North Dakota, and Texas, as well as the Territory of Puerto Rico, are not included in the program.

American Board of Obstetrics and Gynecology, Inc. Examinations

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Saturday, February 12, 1944, at 2:00 P.M.

Arrangements will be made so far as is possible for candidates in Military Service to take the Part I examination (written paper and submission of case records) at their places of duty, the written examination to be proctored by the Commanding Officer (medical) or some responsible person designated by him. Material for the written examination will be sent to the proctor several weeks in advance of the examination date. Candidates for the February 12, 1944, Part I examination, who are entering Military Service, or who are now in Service and may be assigned to foreign duty, may submit their case records in advance of the above date, by forwarding the records to the Office of the Board Secretary. All other candidates should present their case records to the examiner at the time and place of taking the written examination.

The Office of the Surgeon General (U. S. Army) has issued instructions that men in Service, eligible for Board examinations, be encouraged to apply and that they may request orders to Detached Duty for the purpose of taking these examinations whenever possible.

All candidates will be required to take both the Part I examination, and the Part II examination (oral-clinical and pathology examination). Candidates who successfully complete the Part I examination proceed automatically to the Part II examination to be held later in the year.

The Part II examination will be held at Pittsburgh, Pennsylvania, from June 9 to 14, 1944. Notice of the exact time and place of the examinations will be sent all candidates well in advance of the examination date. Candidates in Military or Naval Service are requested to keep the Secretary's Office informed of any change in address.

If a candidate in Service finds it impossible to proceed with the examinations of the Board, deferment without time penalty will be granted under a waiver of our published regulations applying to civilian candidates.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

PAUL TITUS, M.D.

November 16, 1943.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

American Gynecological Society. (1876) *President,* George W. Kosmak, New York, N. Y. *Secretary,* H. C. Taylor, Jr., 842 Park Ave., New York, N. Y. Annual meeting Chicago, May 15, 16, 17, 1944.

American Association of Obstetricians, Gynecologists and Abdominal Surgeons. (1888) *President,* W. R. Cooke, Galveston, Texas. *Secretary,* James R. Bloss, 418-11th Street, Huntington, W. Va. Annual meeting not yet decided.

Central Association of Obstetricians and Gynecologists. (1929) *President,* John H. Moore, Grand Forks, N. D. *Secretary-Treasurer,* W. F. Mengert, Iowa City, Iowa. Annual meeting cancelled.

South Atlantic Association of Obstetricians and Gynecologists. (1938) *President* Oren Moore, Charlotte, N. C. *Secretary,* T. J. Williams, University, Va. Annual meeting cancelled.

A. M. A. Section on Obstetrics and Gynecology. *Chairman,* L. E. Phaneuf. *Secretary,* Philip F. Williams, 2206 Locust St., Philadelphia, Pa. Annual meeting Chicago, May 8-12, 1944.

New York Obstetrical Society. (1863) *President,* W. T. Kennedy. *Secretary,* R. G. Douglas, 530 East 70th St., New York City. Second Tuesday, from October to May, Yale Club.

Obstetrical Society of Philadelphia. (1868) *President,* Catharine Macfarlane. *Secretary,* J. B. Montgomery, 1930 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.

Chicago Gynecological Society. (1878) *President,* George H. Gardner. *Secretary,* Eugene A. Edwards, 104 S. Michigan Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.

Brooklyn Gynecological Society. (1890) *President,* James P. McManus. *Secretary,* William T. Daily, 142 Joralemon St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.

Baltimore Obstetrical and Gynecological Society. (1929) *President,* Lawrence Wharton. *Secretary-Treasurer,* John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.

Cincinnati Obstetrical Society. *President,* Edward Friedman. *Secretary,* Carroll J. Fairo, Cincinnati, Ohio. Third Thursday of each month.

Louisville Obstetrical and Gynecological Society. *President,* Layman A. Gray. *Secretary,* E. P. Solomon, Hegburn Bldg., Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.

Portland Society of Obstetrics and Gynecology. *President,* Howard Stearns. *Secretary,* William M. Wilson, 545 Medical Arts Bldg., Portland, Ore. Last Wednesday of each month.

Pittsburgh Obstetrical and Gynecological Society. (1934) *President,* David B. Ludwig. *Secretary,* Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, February, April, and June.

Obstetrical Society of Boston. (1861) *President,* Thos. Almy, Fall River, Mass. *Secretary,* Paul A. Younge, 101 Bay State Road, Boston, Mass. Third Tuesday, October to April, Harvard Club.

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the name is the year of founding.

New England Obstetrical and Gynecological Society. (1929) *President,* Frank A. Pemberton. *Secretary,* Fred. J. Lynch, 475 Commonwealth Ave., Boston, Mass. Meetings held in May and December.

Pacific Coast Obstetrical and Gynecological Society. (1931) *President,* T. Floyd Bell. *Secretary-Treasurer,* William Benbow Thompson, 6253 Hollywood Blvd., Los Angeles, Calif.

Washington Gynecological Society. (1933) *President,* James R. Costello. *Secretary,* J. Keith Cromer, 1835 Eye St., N.W., Washington, D. C. Fourth Saturday, October to May.

New Orleans Obstetrical and Gynecological Society. (1924) *President,* E. L. Zander. *Secretary,* R. A. Grasser, 2700 Napoleon Ave., New Orleans, La. Meetings held every other month.

St. Louis Gynecological Society. (1924) *President,* S. A. Weintraub. *Secretary,* Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Meetings second Thursday, October, December, February, and April.

San Francisco Gynecological Society. (1929) *President,* R. Glenn Craig. *Secretary,* D. G. Morton, California University Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.

Texas Association of Obstetricians and Gynecologists. (1930) *President,* T. F. Bunkley. *Secretary,* J. McIver, 714 Medical Arts Bldg., Dallas, Tex.

Michigan Society of Obstetricians and Gynecologists. (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President,* Norman F. Miller. *Secretary,* Milo R. White, 2799 W. Grand Blvd., Detroit, Mich. Meetings first Tuesday of each month from October to May (inclusive).

Obstetric Society of Syracuse Hospitals. (1938) *President,* Edward C. Hughes. *Secretary,* Nathan N. Cohen, 713 E. Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May. Suspended for the duration.

Alabama Association of Obstetricians and Gynecologists. *President,* J. M. Weldon, Mobile, Ala. *Secretary,* Eva F. Dodge, Montgomery, Ala.

San Antonio Obstetric Society. *President,* I. T. Cutter. *Secretary,* S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.

Seattle Gynecological Society. (1941) *President,* Carl M. Helwig. *Secretary,* Gerhard Ahnquist, 1336 Madison Street, Seattle. Meetings third Wednesday.

Denver Obstetrical and Gynecological Society. (1942) *Secretary,* Emmett A. Mechler, 1612 Tremont St., Denver, Colo. Suspended during war.

Wisconsin Society of Obstetrics and Gynecology. (1940) *President,* Roland S. Cron. *Secretary,* Robert E. McDonald, 425 E. Wisconsin Ave., Milwaukee, Wis. Meetings held in May and October.

San Diego Gynecological Society. (1937) *President,* Geo. D. Huff. *Secretary,* Frank Russell, 233 A St., San Diego, Calif. Meetings held on the last Wednesday of each month.

North Dakota Society of Obstetrics and Gynecology. (1938) *President,* John D. Graham, Devil's Lake. *Secretary,* G. Wilson Hunter, 807 Broadway, Fargo, N. D.

Virginia Obstetrical and Gynecological Society. (1936) *President,* A. L. Carson, Jr. *Secretary,* L. L. Schamburger, 628 State Office Bldg., Richmond, Va. Next meeting not announced.